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NEPHRITIS
ITS PROBLEMS AND TREATMENT

T. IZOD BENNETT

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NEPHRITIS
ITS PROBLEMS AND TREATMENT

BY

T. IZOD BENNETT

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PREFACE

THE more closely a medical man has studied nephritis the more readily will he agree that the subject is almost as bewildering to the expert as it is to the junior medical student. Nothing indeed save ignorance can excuse the physician who is ready to profess himself satisfied with our present knowledge of the subject.

Bright taught us that certain clinical states were associated with certain morbid changes in the kidney, but it has long been apparent to every clinician interested in pathology that existing attempts to classify nephritis according to naked-eye appearances found in the post-mortem room have failed to give a satisfactory basis to our knowledge.

It seems possible that morbid anatomy, at any rate macroscopic anatomy, is reaching the limits of its usefulness in these diseases, and that the study of disorders of function, as revealed by clinical and laboratory investigations, is now the most promising avenue of approach. In addition, it is clear that inquiry must embrace many tissues beside the kidneys before satisfactory knowledge is attained. To stand at the bedside of an anasarcous patient and talk of large white kidneys is a somewhat vain proceeding, whilst increasing knowledge of hypertension and its consequences has already driven the granular kidney to a position more worthy of its importance.

This book is based on three lectures delivered before the Royal College of Physicians in the Spring of 1928, in which the problems of uraemia, of oedema, and of hypertension were discussed. I have now made certain additions and alterations which may provide a more harmonious survey of a subject which is inexhaustible, and I hope that I may thereby present to readers interested in clinical medicine and medical science a basis for reflection.

I take this opportunity of thanking the President and Fellows of the Royal College of Physicians for the honour

done me in inviting me to deliver the Goulstonian Lectures. I have had help from so many of my colleagues at the Middlesex Hospital that it is not possible to express my indebtedness to each of them, but from Professor E. C. Dodds and Dr. Evan Bedford I have received so much assistance that special acknowledgement must gratefully be made.

T. I. B.

London, W.1,
January 1929.

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CHAPTER I

INTRODUCTORY

NEPHRITIS as it presents itself to the student or to the practitioner is a syndrome comprising one or more of the following features: albuminuria, haematuria, oedema, hypertension, and that group of phenomena described as uraemia.

There are many other signs and symptoms seen in nephritis, but those enumerated above are the cardinal ones on which the diagnosis is based. Several or all of them, as has been said, may be present in any one particular case. The diagnosis is seldom certain if only one is present, and it is not my purpose in this book to discuss in any detail the reasoning by which an exact diagnosis can be arrived at in the absence of abundant signs and symptoms.

I wish rather to give the reader an opportunity of forming a useful opinion with regard to diagnosis, prognosis, and treatment, when confronted with a typical case of nephritis in any of its multiple forms.

Let it be imagined, for example, that the practitioner is confronted with a young adult patient who complains of generalized oedema with breathlessness, and is found on examination to have a definite elevation of blood-pressure, a somewhat hypertrophied heart, and urine containing albumin but no blood. Such a case would without hesitation be labelled as nephritis, but to pass on from that to a more exact diagnosis, to make a prognosis of any accuracy, and to prescribe the most useful treatment, is a task which it is to be feared is beyond the power of many medical men.

Our difficulties are increased by the fact that classifications of nephritis vary from text-book to text-book in a bewildering manner. Few, if any, of them conform to the facts of nephritis as known to the clinical observer, and most of them are admitted by morbid anatomists to conflict with post-mortem experience. I shall in a later chapter attempt to

set out what I believe to be a working classification, but it seems preferable at this stage to examine the problem from the clinical point of view alone. In succeeding chapters will be found a discussion of the problems of uraemia, of oedema, and of hypertension, for, if a clear conception of these problems can be obtained, it would seem that the outlook on any ordinary case of nephritis will thereby be simplified.

Albuminuria.

Clinical experience teaches us that albuminuria almost invariably accompanies nephritis. It may, however, occur in the absence of renal disease. Albuminuria appearing in the course of pregnancy carries with it the suggestion of threatened nephritis, and again when any acute infectious fever is complicated by the appearance of albuminuria, the possibility of acute nephritis presents itself. It is not, however, customary to make a definite diagnosis of nephritis in such cases unless some other sign or symptom, such as haematuria with oedema or elevation of the blood-pressure, becomes manifest.

Albuminuria is occasionally the only abnormality discoverable in patients who are apparently in good health. Cases are sometimes seen in which such albuminuria may be very heavy. It becomes a matter of excessive difficulty to decide whether these cases have renal disease, and if so what its nature may be.

Looking at albuminuria from another point of view it is not at present possible to speak with precision as to the exact nature of the protein present in the urine in such cases. To regard it simply as the serum albumin of the blood is an elementary error. Available methods of analysis are insufficient to supply full information on this point. When again we ask what is the exact mechanism by which protein passes from the blood serum to the urinary tract, no answer is available, and when the extreme degree of proteinuria met with in certain rare cases is contrasted with the apparent

good health of the patient, the difficulty of finding a plausible explanation is very great.

From these facts it is clear that the subject of albuminuria itself presents many difficulties, but it is not proposed to discuss them at any length in this volume. In later chapters some of these problems will be set out more fully, but always in connexion with clinical varieties of nephritis in which albuminuria is one of several manifestations.

Renal Disease and Renal Failure.

If a case of nephritis is to be dealt with efficiently it is necessary that at the outset an opinion should be formed as to whether renal failure, either temporary or permanent in nature, is present. Disease of the kidney of considerable degree and possibly of progressive character may be present for years without renal failure occurring, but it is also possible for renal failure to make its appearance as the first sign that any renal lesion is present.

The matter may perhaps be best explained by reference to certain well-known experiments. When double nephrectomy is carefully performed upon an animal, it is possible for it to recover from the operation and remain apparently in complete health for a brief period, after which renal failure, usually manifesting itself by uraemic symptoms, appears and rapidly terminates life. If, however, one kidney is entirely removed and a part only of the other organ is excised, the appearance of renal failure will depend strictly on the amount of tissue removed from the second kidney. If sufficient kidney substance has been left, the animal will continue in good health unless and until destruction, following inflammatory reaction from the operation, has done away with a sufficient amount of the remaining renal tissue.

By experiments of an entirely different nature, such as the administration of uranium salts or of perchloride of mercury, it is possible to produce in animals some of the phenomena

which we associate with inflammation of the kidneys in man without at once producing renal failure.

On p. 7 and p. 47 the reader will find a further description of the nature of renal failure. It is necessary to realize that the phrase implies that so great a proportion of the total kidney substance has been destroyed or rendered inactive that it is impossible for the remaining tissue to carry out its functions. *It is by no means necessary for nephritis to be present in order for this to happen.* Non-inflammatory diseases such as cystic disease of the kidneys, neoplasms, or calculous obstruction may equally well produce such destruction that renal failure results.

Renal Efficiency Tests.

Tests of renal efficiency are designed with the object of obtaining information on this point. The failing kidney will at first give evidence of a diminished capacity to secrete the nitrogenous constituents of the urine in their usual concentration, and it will at a later stage be unable completely to remove excess of these substances from the blood. In the former circumstances the test which will reveal early renal failure is *observation of the specific gravity of the urine.*

Certain life assurance companies refuse policies to patients who are unable to pass urine whose specific gravity exceeds 1,015, and it is possible that observations of specific gravity present the most delicate method available for testing the concentrating power of the kidney. The healthy individual passes urine the specific gravity of which varies at different hours of the day through a very wide range, according to his food and water intake. After taking a lot of fluid it will fall to 1,012 or lower. After a large protein meal it will rise considerably above 1,020, the variation in concentration being evidence of the kidneys' capacity to eliminate water or urea and other nitrogenous bodies from the urine in the manner most advantageous to the body, for the purpose of maintaining the volume and constitution of the blood at an optimum.

When doubt exists as to the functional capacity of the kidney, the test can be carried out as follows:

The patient is instructed to empty the bladder on waking in the morning, and is then given a hearty breakfast containing, for example, fish or eggs and bacon with plenty of toast, butter, and jam, but not more than the minimum quantity of fluid in the form of tea or coffee necessary to enable him to swallow his food. An hour or two later the urine is collected and, should its specific gravity then be lower than 1,020, the presence of renal failure is more than probable. Should the specific gravity be below 1,015, it is certain that renal failure is present.

Similar information is obtained by the **Urea Concentration Test,** which has been popularized by Professor MacLean of St. Thomas's Hospital. This test is carried out as follows:

After emptying the bladder the patent swallows 15 grammes of urea dissolved in water, and specimens of urine are collected one hour and two hours afterwards. The urea in these specimens is estimated and in normal persons should reach a concentration of at least 1·5 per cent. in the first specimen and 2 per cent. in the second specimen. The results given by this test appear to be equally but not more satisfactory than those given by careful estimation of the specific gravity following a dry meal.

On page 47 will be found a description of the manner in which the failing kidney, unable to secrete nitrogenous bodies in a high concentration, can nevertheless remove its daily quota of waste material from the blood by secreting large volumes of dilute urine. In time this state of *compensated renal failure* progresses to one in which accumulation of waste nitrogenous constituents becomes manifest in the blood. This will be revealed by **blood analysis.** Reference to later chapters will, it is hoped, make clear the importance of frequent observations on the chemistry of the blood in the study of any case of nephritis. Even when the figures so obtained are normal, they are often of great value for com-

parison with those obtained at a later date. For the moment we are only concerned with the value of blood analysis in revealing renal failure, and in the following table are set out the figures found in normal subjects and in those in whom failure of the kidneys is definitely present.

TABLE I.—BLOOD ANALYSIS*

	Normal.	*Renal Failure.*
Urea	25–40	50–200 or more
Non-protein Nitrogen .	20–40	50–200 or more
Uric Acid . . .	2–3	4–10
Creatinin . . .	1·0–1·5	2–10
Amino-acid Nitrogen .	4–7	8–14
Chlorides (as NaCl) .	below 580	?
Phosphates (as P_2O_5) .	below 4	4–9
Calcium . . .	10–12	reduced

It must be emphasized that such evidence denotes a high degree of renal failure. That is to say, renal failure may be present and demonstrable before such changes become apparent. On the other hand, nitrogen retention in the blood does not necessarily mean *permanent* renal failure, for it may occur as a transient phenomenon during some acute process which will subside and leave the kidneys relatively unimpaired.

Having gathered information as to the renal capacity in any given case, the observer can turn his attention to the questions as to whether the case is an acute one, a recurrent one, or a chronic one, and can proceed to form an opinion concerning what the future progress will be and what may be the appropriate treatment. Such an opinion must be based on knowledge concerning the great problems of nephritis which are dealt with in subsequent chapters.

* In this and subsequent tables figures, unless otherwise stated, represent milligrams per 100 c.cm.

CHAPTER II

THE PROBLEM OF URAEMIA

THE more one studies nephritis, the more is one aware of the extreme complexity of the subject, and any attempt to review the problems of uraemia must be tentative, although recent work has thrown new light on the mechanism governing some of the phenomena which we group together under this heading. A great variety of symptoms is by different writers included under the heading of uraemia, and at the outset we must make distinction between those which occur where both ureters became simultaneously blocked, or when a single functional kidney is accidentally removed, and the train of symptoms which characterizes the termination of a case of nephritis. The former syndrome is usually marked merely by slowly deepening coma, whilst in the latter are seen, in classical form, not only the gastro-intestinal symptoms, but also the muscular twitchings, the convulsions, and often the hyperpnoea, which form for most of us the picture of true uraemia.

I propose to describe some typical biochemical observations from a case of this latter type, and after endeavouring to demonstrate those aspects which I feel to be of true importance in the production of the peculiar nervous phenomena of uraemia, I shall describe some recent experimental work which appears to be relevant in this connexion.

A Case of Renal Failure.

The original custom for the Goulstonian lecturer to give a demonstration on some dead body, 'to be then and there dissected for the disease treated in the lectures', has for many years fallen into disuse. But I may perhaps be permitted to begin this chapter by describing a case which illustrates in many details the problems of uraemia.

The patient, a woman then aged 42, came under my care in 1923 complaining of abdominal discomfort associated with a

tumour in the right side which was rapidly increasing in size. Albumin was present in small quantities in the urine, and the blood showed marked retention of nitrogen. It was decided after consultation that an exploratory operation should be performed. This was carried out by my colleague, Mr. John Murray, and revealed extensive cystic disease of both kidneys, although the left was so much less enlarged than the right that it had not been palpable before operation. The incision was closed and nothing further was done, recovery from the operation being quite straightforward.

At her earnest request a clear explanation of the condition and its probable consequences was made to the patient, who was a person remarkable both for her intelligence and philosophy. For two years already she had complained of constant dryness of the mouth with a peculiar taste, as well as of some diminution in her bodily strength. She was advised to abstain as much as possible from foods containing a large proportion of protein, and returned to her home. Two years later she consulted me again and was placed on a diet containing a very high proportion of carbo-hydrates. At this time the right kidney had increased considerably in size and the left had become readily palpable. There was considerable loss of strength, so that she was obliged to lead the life of a semi-invalid, rising for not more than six hours daily and seldom walking as much as one mile on any day. She returned home, where she lived chiefly upon green vegetables, biscuits, and farinaceous food, and gradually declined in vigour until the middle of last summer, when she again came into hospital for closer observation. I feel it my duty to record the fact that this lady was so desirous to be in any way of service to others who might be ill, that for four years she placed herself at my disposal for any investigations which I might feel to be of possible utility.

At the time of her final admission to hospital in the summer of 1927 her appearance was, on the whole, healthy, although there was a slight puffiness below the eyes, and the legs, although not pitting on pressure, had a somewhat swollen appearance. She was rather deeply freckled and pigmented, which made her aspect deceptively healthy, for she was so weak that it was impossible for her to walk more than 100 yards, and dyspepsia with occasional vomiting, together with attacks of breathlessness during the night, were making her life uncomfortable. Although she could give an astonishingly clear account of her symptoms, she stated

that her brain felt as if it were in a fog, and that consecutive thinking was difficult to her. She gave a graphic account of the constantly bitter taste of her saliva, and complained of a frequent sinking feeling and faintness between meals. On examination there was no obvious hypertrophy of the heart, though the blood-pressure was 100 diastolic and 180 systolic. The renal tumours were very large, distending both flanks; the right remained larger than the left. Polyuria was present, but disturbed her very little, and her sight was entirely unimpaired, there being no changes whatever in the fundus oculi.

Treatment and its Effects

My first endeavour was to alleviate her nausea and tendency to vomit, and this was accomplished by still further curtailing her diet, so that she lived for several weeks on nothing but tea without milk, orange juice, and dry biscuits, the total value of the diet being something less than 600 calories a day. On this her gastro-intestinal symptoms were indubitably less acute, but she was hungry and felt her weakness to be increased, and I was accordingly obliged to revert to the somewhat more generous diet she had previously taken. Her condition as regards nitrogenous bodies in the blood up to this time is shown in Table II.

TABLE II

	Dec., 1923.	*March, 1925.*	*Oct., 1926.*	*June, 1927.*	*Sept., 1927.*	*Oct., 1927.*
Blood-urea .	50·6	64	68	105	90	146
Non-protein N.	41·9	84	52	75	90	108
Creatinin .	1·8	2·1	2·5	3·4	4·6	6·1
Uric Acid .	2·9	3·6	4·8	—	3·8	2·6

These figures also show the upward trend of the commoner nitrogenous bodies up to the time of her final admission. The last three columns suggest that the very restricted diet had exerted some influence in reducing the concentration in the blood, but this possible improvement was abruptly lost, as shown by the high figures in the last column, when the more generous diet was resumed. Until the end of October the clinical condition was unchanged and arrangements were then made for the patient to return to her home.

The Final Phase

In a recent essay dealing with the phenomena of uraemia Sir John Rose Bradford described the abrupt and dramatic violence which sometimes characterizes the onset of the final uraemic symptoms. Such was my experience in the present case, for in the early morning of Nov. 2nd, 1927, the patient was seized with violent convulsions followed by unconsciousness. Within an hour she had apparently recovered and, though a little frightened, gave a clear account of her symptoms and described how the twitching of her muscles, which was now very apparent, had first been observed on the previous day, when some stiffness of the limbs and occasional aching in the back had troubled her. The blood-pressure remained in the region of 150 mm. systolic, and a full half-litre of urine was passed. This condition, of clear consciousness with sharp twitchings of the muscles, remained unchanged for a further 24 hours, and it is worthy of mention that her mental state was one of entire comprehension of her situation; she talked cheerfully and with full intelligence, and was at pains to call the Sister of the ward and to give instructions that both my friend, Professor E. C. Dodds, and myself were to be allowed to take any specimens of blood or cerebro-spinal fluid we might desire at any time, and that we were to have full liberty to carry out complete post-mortem examination if she should not survive.

During that night several severe fits occurred, between which the patient was only semi-conscious, and the muscular twitchings were very noticeable. She complained of extreme pain in the back, apparently due to the convulsive contraction of the erector spinae muscle. Calcium lactate in doses of grs. 5 and sodium bicarbonate in doses of grs. 60 were given hourly during the following day, and more than one pint of urine was passed during the same period.

Apparently as the result of this treatment, consciousness was regained, and during the next 24 hours twitching was less marked; the patient could reply to all questions, although her mental state was very confused. She drank fluids freely, and passed fair amounts of urine, although incontinence was present. Drowsiness reappeared on the night of Nov. 5th, and convulsions became frequent, with almost complete unconsciousness between the attacks. It was felt that there was no justification in proceeding to intravenous medication and, therefore, no further alkali was given during the day of Nov. 6th, when the patient lay in coma. One convulsion occurred at 6 p.m., and death followed an hour later.

The following table shows the nitrogenous constituents of the blood during this last phase.

TABLE III

	Nov. 2nd.	*3rd.*	*4th.*	*5th.*	*6th.*	*7th (p.m.).*
Blood-urea . .	257	321	356	292	367	357
Non-protein N. .	215	241	260	220	277	272
Creatinin . .	7·5	6	6·5	6·5	7·4	9·2
Uric Acid . .	8	7·2	7·3	9·6	14	9·6
Amino-acid N. .	6·2	6·8	5·9	5·2	7·4	12·8

Commentary. This case has been selected purposely as illustrating several important points. In the first place, it seems of value in that it is an example of pure and progressive renal failure terminating in uraemia, without being a case of true nephritis. Short of deliberate experiment, it is difficult to imagine circumstances by which the effects of slow destruction of kidney substance could be produced as accurately as is done by this strange disease.

It is not here proposed to enter into discussion of the pathology of cystic disease, for it is impossible yet to formulate even a plausible theory to account for this affection, but it may be permissible to consider in detail the main symptoms which affected this patient, with a view to deciding to what degree we can explain the mechanism by which they were produced.

Until the last four days of her life she was really seriously troubled by two sets of symptoms only: first, those of progressive weakness; and secondly, nausea, anorexia, and especially a foul and bitter taste in the mouth. It is plausible to suggest that the weakness was largely the result of the low diet on which she was obliged to live, whilst the disorders of appetite and taste were almost certainly the result of the over-saturation of the blood with urea and kindred nitrogenous substances. The account of the taste, given by the patient, was a very exact description of that of urea, and the

following analysis of her saliva, compared with that of normal persons, as reported by Dodds, supports this belief very strongly.

TABLE IV.—*Analysis of Nitrogenous Constituents of Saliva.*

	Ammonia (as N.).	*Urea.*
Normal average . .	6·3	9
Uraemic patient . .	75·0	41

It is perhaps of particular interest that neither oedema nor hypertension was present in more than slight degree, but to these facts further reference will be made later.

Returning to the events of the last five days of her life, we are faced with the classical phenomena of acute uraemia, with its two customary and interwoven symptoms—convulsions and coma. These symptoms are clearly referable to the central nervous system, and with them we must discuss the muscular twitchings which were a prominent feature of the terminal period, even at times when the brain was clear. The progressive coma typical of calculous anuria and of complete excision of the kidneys has long been distinguished from the twitchings and fits of certain other cases. Possibly the present case should be regarded as exhibiting both these types intermingled. But it is essentially the muscular twitchings and convulsions which place the present case in the category of true uraemia, and we must now inquire to what extent these symptoms can be explained by observations on the changes in the body fluids which occur in such subjects.

Nitrogen Retention.

Perhaps the most popular explanation of uraemia is that it is the direct result of the accumulation of urea and kindred substances in the blood. Bright himself was to some extent the originator of this theory. In his Goulstonian lectures, delivered in 1833, he said: 'What seems in some way to

account for the general derangement and suffering of the constitution is the fact that urea becomes demonstrable in the circulating mass, and the blood becomes impregnated with that substance.'

In the ninety-six years which have followed, this conception of the significance of urea retention has been amplified. We have learnt that urea is but one of the nitrogenous bodies which accumulate in the blood in nephritis, and we have learnt that a similar retention occurs in the case of certain non-nitrogenous substances. Towards the beginning of the present century the study of this aspect of nephritis was given a fresh impetus by the work of Widal and Javal, who introduced more accurate methods of blood analysis, and of Achard, whose recent summary of the subject is a model of clear exposition. This work appears to have focused the attention of many French observers to an extent that is perhaps excessive. For though we all realize to-day that the retention of nitrogenous substances in the blood is an invaluable help in the diagnosis of renal failure, and though we appreciate the fact that high nitrogen figures may become of great prognostic importance, we also realize that *nitrogen retention by itself offers no explanation of the actual phenomena of uraemia.* Without entering into the bulky literature of this subject, the chief reasons against nitrogen retention being the cause of uraemia may be summarized as follows.

1. The administration of urea and kindred substances to animals does not produce uraemia.

2. Conditions such as cystic disease of the kidney or prostatic obstruction often persist for years with marked nitrogen retention but no evidence of uraemia.

3. Cases of uraemia without nitrogen retention are occasionally observed.

Retention of Non-Nitrogenous Substances.

The retention of nitrogenous substances in the blood is marked in renal failure largely because they are quantita-

tively amongst the more important substances which the kidney is normally called upon to excrete; but evidence accumulates to show that other chemical substances will show increased concentration in the blood, although to a lesser degree. Thus de Wesselow has published interesting observations on the high concentration of phosphates seen in uraemic patients, and in a more recent study he has confirmed and elaborated the work of other observers which demonstrates that even sodium chloride is excreted with difficulty and tends to show an increasing concentration in the blood in these cases. The blood analyses in the case described above were in full agreement with these findings, the actual figures in the terminal phase being as follows:

TABLE V

	Blood phosphorus (*normal*, 2–3).	*Blood chlorides* (*normal, about* 500).
Nov. 2nd . . .	6·3	503
„ 4th . . .	6·2	561
„ 5th . . .	8·5	568
„ 6th . . .	8·5	553

Andrews has recently called attention to a curious diazo-reaction given by the blood and cerebro-spinal fluid in cases of uraemia; this reaction was positive also in my case. It has been shown by Blotner and Fitz to appear rapidly in dogs after nephrectomy, and though its significance is still obscure, it seems very possible that this again is an example of the retention and concentration in the blood of some substance which the normal kidney would excrete. Whilst admiring the patience and ingenuity with which biochemists have inquired into these problems, we are bound, I think, to admit reluctantly that at present no direct relation has been shown to exist between the accumulation of any of the chemical bodies I have discussed and the nervous phenomena of uraemia.

Acidosis in Uraemia.

If we now turn our attention to other aspects of the blood chemistry in renal failure, we find that acidosis is almost invariably an accompaniment of this state. The word acidosis being here used, in accordance with the suggestion of the Medical Research Council, to denote a lowering of the alkali reserve of the blood.

The work of Palmer and Henderson, of Weil and Guillannin, of Mogena and Orcoyen, may be quoted as typical observations amongst many which confirm the view that acidosis can be demonstrated in all cases of uraemia in which nitrogen retention is present and especially in those with marked nervous and respiratory symptoms. My patient with cystic disease of the kidneys was no exception to this rule, for the alkali reserve estimated shortly after the onset of her terminal symptoms stood at the low figure of 12·6, and subsequent estimations are shown in the following table:

TABLE VI.—*Alkali Reserve in c.cm. of CO_2 per 100 c.cm. Plasma.*

Nov. 2nd . .	12·6	Nov. 5th, 10 a.m. .	48·5
,, 3rd . .	13·7	,, 5 p.m. .	55
Nov. 4th, 5 a.m..	20·9	Nov. 6th, noon . .	56
,, 10 a.m..	28·7	,, 7th (autopsy) .	18·2
,, 9 p.m..	36·8		

The gradual increase in the alkali reserve which occurred in later days was the result of the administration of large doses of sodium bicarbonate which was instituted about 12 hours after the first convulsion. The effect on the patient's general condition was very marked at first, but passed off after the third day. Muscular twitchings never completely disappeared, although they became less noticeable, the general effect being a restoration to full consciousness. It must, however, be observed that this amelioration was only

temporary, that the muscular twitchings were never entirely suppressed, and that, in spite of the improvement in the acidosis, coma and convulsions returned and became irremediable. The logical conclusion is that the condition of the blood alkali is not by itself a cause of the neuromuscular phenomena, and the absence of such symptoms in other conditions of acidosis makes it probable that here once more we have been following a false trail.

Possible Importance of Calcium.

If we resume our search for a chemical explanation of uraemia, having discarded those substances which are in excess in the blood and having put aside acidosis as an explanation, is there any other feature of the blood chemistry which may possibly throw light on the problem? Blood analysis is usually confined to a limited group of substances, but there is one amongst them not yet examined which may have an important bearing on uraemia. I refer to calcium. We are here on very difficult ground, for though actual estimation of the calcium content of blood is not unduly difficult, the problems surrounding the actual physical state of calcium in the blood, the relation, for example, between the ionized and total calcium, are extremely intricate, so that an interpretation of the figures is at present very nearly impossible. In the work of de Wesselow already quoted, attention was drawn to the diminution in the calcium content of the blood which accompanied the increase in the phosphates. Such a diminution was very marked in this case of cystic disease, the calcium of the blood, which is normally from 10–12 mg. per 100 c.cm., being reduced to 6 mg. or even less. This low figure was found to persist throughout the terminal phase of the patient's illness, and was not apparently influenced by the improvement in the acidosis which followed the administration of sodium bicarbonate. The actual calcium figures are shown in the following table:

TABLE VII.—*Calcium Content of Blood.*

Normal average . . .	10–12.		
Uraemic patient:		Nov. 5th . . .	6·5
Nov. 2nd . . .	6·6	Nov. 6th . . .	5·9
,, 4th . . .	6·5	Post mortem . .	8·9

It has already been said that in the present stage of our knowledge it is impossible to draw any permanent conclusion as to the meaning of these low calcium figures in uraemia, but reflection on the phenomena observed in certain other clinical states in which the calcium of the blood is reduced is somewhat suggestive.

Tetany.

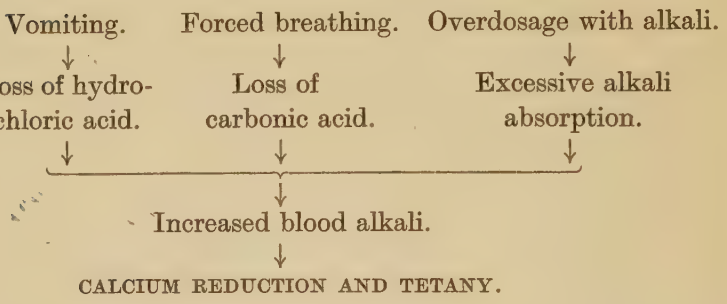
The group of cases in which a distinct reduction of the blood calcium is most marked is that in which are to be seen the symptoms described as tetany, and tetany is found to occur in a large number of apparently dissimilar diseases, the chief of which are: (*a*) non-malignant pyloric stenosis; (*b*) parathyroid deficiency; (*c*) chronic diarrhoeal states; (*d*) rickets; (*e*) poisoning by overdosage with alkalis.

I recall, for example, an interesting patient with pronounced vomiting as the result of pyloric obstruction of obscure origin. She suffered from tabes, and was at first believed to have gastric crises; but fuller investigation showed that practically nothing could ever pass through the pylorus. The barium meal upset her greatly, and after several hours, during which she was in a semi-fainting condition, she exhibited muscular irritability, and I was called to her at a time when she lay in a condition of complete carpopedal spasm with the classical flexion and extension of joints characteristic of severe tetany. A subsequent operation revealed a curious thickening at the obstructed pylorus which was possibly of gummatous origin.

Amongst other causes of tetany we must note that it has been produced experimentally in man by forced breathing

over long periods, and in certain cases where the therapeutic administration of alkalis has been pushed to an extreme point. In such examples it is easy to demonstrate certain chemical factors which are constantly present. These are indicated in the accompanying table.

TABLE VIII



It will be seen from examination of this table that all the cases in this group have three factors in common: first, alkalosis; secondly, tetany; and thirdly, a reduction in the calcium content of the blood.

Reverting to the conditions in which tetany is commonly encountered it is well established that some connexion often exists between this condition and a deficiency of the parathyroid glands; its occurrence in certain diseases of children, such as rickets and coeliac disease, is also well known; whilst even in adults it is an occasional finding in conditions of chronic diarrhoea. Dr. Jean-Charles Roux recently showed me a very interesting case at the Hôpital Vaugirard in Paris. The patient was a woman who for many years had had constant diarrhoea, with loose stools containing a large proportion of all the ingested fat. The pathology of the case was obscure. For many months she had suffered from tetany, often latent, but sometimes showing itself acutely; its main manifestations were always rapidly relieved by any one of the following agents: (*a*) cod-liver oil emulsion; (*b*)

irradiation with ultra-violet light; (*c*) calcium and parathyroid medication.

There is probably a common action to each of these three forms of treatment, and this action may be briefly defined as *fixation of calcium*. Such a view is supported by the current conception that calcium shortage is the one common factor in all forms of tetany, and it is worth considering whether it is not possible that a true relationship may exist between the twitchings and convulsions of uraemia—which, as we have seen, are associated with a low calcium content of the blood—and the nervous phenomena known as tetany, in which calcium shortage appears to be the outstanding chemical feature. I have indicated that acidosis is usually prominent in uraemia, and we have gone on to note that alkalosis is often very marked in tetany, but that a disorder of calcium metabolism seems to be common to the two states, and that there is a close resemblance between the neuromuscular phenomena seen in the two syndromes, has not always been recognized.

Renal Disease of Gastric Origin.

Having drawn attention to this suggestive similarity, we may now consider for a moment whether there may not occasionally be an even closer association between gastric and renal disease than has usually been recognized.

TABLE IX

Progressive Renal Disease.	*Non-malignant Pyloric Obstruction.*
Acid accumulation in blood.	Acid loss from vomiting.
Acidosis.	Alkalosis.
Phosphorus retention.	Chloride loss.
Nitrogen retention.	Nitrogen retention.
Calcium reduction.	Calcium reduction.
Twitchings and convulsions.	Tetany.

In Table IX I have set out some of the outstanding features

in (*a*) cases of advanced renal destruction, and (*b*) cases of pyloric obstruction with tetany. Reference has already been made to an example from the latter group, and I am indebted to Dr. Hinds Howell for the information that later, whilst under his care in St. Bartholomew's Hospital, before an operation for the relief of her pyloric obstruction, this patient exhibited persistent albuminuria with hyaline and granular casts. Brown, Hartman, Eusterman, and Rowntree, and Zeman, Friedman, and Mann have reported a series of cases of pyloric or upper intestinal obstruction, usually accompanied by tetany, in which routine histological examination of kidneys removed at autopsy showed entirely unsuspected changes, of a markedly degenerative nature, in the renal tubules. These changes were of the type seen in cases of mercurial poisoning, and Crohn reports the case of a patient who had undergone an operation for pyloric obstruction and in whom uraemia, resulting from this renal complication, was the cause of death. This rare group of cases is a very instructive one in reminding us that *not only will renal damage produce profound changes in the blood chemistry, but that chemical changes in the blood may themselves exert a destructive effect upon the kidney substance.*

Some Experimental Work.

It will perhaps be valuable if attention is now diverted from these purely clinical and biochemical observations to some recent experimental work which seems of great importance in connexion with the problems of uraemia. Of particular interest are certain experiments which have been performed in connexion with the rapid ingestion of large quantities of water in animals. In normal circumstances we are protected against a too rapid absorption of water by a series of physiological mechanisms. In the first place, thirst is quickly replaced by satiety, and even if these natural instincts are forcibly overcome the pylorus will by complete closure prevent the entrance of water into the small intestine

after a certain amount has been let through. Overloading of the stomach with water is soon followed by vomiting and thus any excess in the small intestine is prevented. It would seem that there is little limit to the speed with which the small intestine can absorb water, but the renal mechanism by which it is removed from the circulation is also a rapidly acting one, and, therefore, provided that the pyloric valve exerts some degree of control it is impossible in ordinary circumstances to produce a true plethora of water in the circulation.

Rowntree and others have, however, by passing tubes through the pylorus in animals, succeeded in introducing water so rapidly into the small intestine that it was absorbed into the blood-stream quicker than the animal's kidneys could remove the consequent surplus. A very interesting series of events then occurred, the animals under investigation exhibiting twitchings and strychnine-like convulsions which rapidly passed on to coma and death. It is difficult when reading the accounts of these experiments to find any distinction between the symptoms of such animals and those of patients suffering from renal failure. No one, so far as I know, has dared to attempt the reproduction of these experiments on men, but it is worthy of note that in diabetes insipidus a sudden arrest of the polyuria produced by means of the administration of pituitary extract has in some instances been followed by the appearance of giddiness, twitching, and fainting, symptoms which never occur in these circumstances if the intake of water is reduced before the injection of pituitary extract.

The most recent experimental work dealing with uraemia is perhaps less convincing because of its complexity, but close examination shows that it is probably of extreme importance. Working with dogs, E. Andrews has shown that when the alkali reserve of the blood is low the injection of salt solution into the circulation fails to produce diuresis. After a short period muscular twitchings appear, and from this the animals

pass on to a condition in which repeated convulsions terminate in coma, hyperpnoea, and death. Examination of the blood of these animals showed definite nitrogen retention, post-mortem examination of the animals' brains demonstrated oedema, but the kidneys on microscopic section were found practically normal.

Neglecting for the moment the observations of Andrews on other aspects, it would seem that by these experiments a syndrome indistinguishable from that of uraemia is produced by the injection of sodium chloride solution in the presence of acidosis, without any renal lesion being present before or after. And it is worthy of interest that this worker reaches the conclusion that it is largely owing to the disturbance of calcium metabolism that the convulsive symptoms are produced. In an incomplete, but suggestive, series of experiments he has been able to suppress the convulsions of these animals by the intravenous administration of calcium in large doses.

Conclusion.

I have now touched on many of the chemical factors which, at the present stage of our knowledge, appear to be of major importance in the problem of uraemia. That my review must be incomplete I am well aware. And particularly I am conscious of two very important omissions: first, no reference has been made to the relative conditions of the blood and of the cerebrospinal fluid; and, secondly, I have not endeavoured to deal with cerebral oedema as a possible factor in the production of uraemia.

As regards the cerebrospinal fluid, it is obvious that by studying its chemical state we have better knowledge of the chemical conditions in the central nervous system than if we study the blood alone; but the difficulty of collection is a great handicap in such investigations, and has prevented that frequent repetition of observations which is so easy in the case of the blood. The analyses which were secured on the

cerebrospinal fluid in the case of my patient with cystic disease gave figures similar to those in the blood, so far as we could ascertain, but usually less marked in degree, there being probably some lag in the appearance of concentrated retention products in the central nervous system; but the impossibility of taking many specimens makes me hesitate to speak more precisely than this. To cerebral oedema I shall refer in a later chapter; for it seems appropriate to discuss this question when dealing with the general problem of oedema.

In the study of medicine we should, said Bright, cultivate a chastened power of generalizing our ideas. And if this chapter has dealt with chemical more than with anatomical peculiarities it is because I feel that it is in that direction that we can most fruitfully pursue our inquiries into the problem of uraemia. Ninety-six years ago, when delivering the Goulstonian lectures, Bright again and again dwelt on the importance of the chemical aspects of these problems. 'If the deranged action of the kidneys', he said, 'continue long, the urea can be detected by the chemist's art in the course of the circulation,' and in later passages he gave full credit to his friend, Mr. Rees, who was 'ardently pursuing the subject of animal chemistry'. To-day we are no less dependent on the help of our friends in the laboratories, and I feel it proper to conclude this chapter by expressing my indebtedness to that group of colleagues from whom I have always received such unselfish assistance in the exploration of these difficult problems.

CHAPTER III

THE PROBLEM OF OEDEMA

'When albumen is proved to exist in the urine I look upon it with anxiety, and the confirmed derangement I always view with dread.'—R. BRIGHT, Goulstonian Lectures, 1833.

THE problems of so-called 'renal' oedema are of even greater complexity than those of uraemia. The work of the chemical and experimental laboratories has advanced to a degree that makes it quite impossible for any man to form a useful judgement on such subjects from the result of his personal observation alone, and the intricacy of many of the researches into oedema is such that the wheels of the intelligence become almost clogged in the effort of sifting the important from the insignificant facts; but close study leads one to the conclusion that WHEN OEDEMA OCCURS IN A CASE OF NEPHRITIS IT IS EVIDENCE OF THE EXISTENCE OF AN EXTRA-RENAL FACTOR WHICH MAY EXPLAIN THE NEPHRITIS, BUT IS NEVER THE CONSEQUENCE OF NEPHRITIS. We speak of 'renal' oedema, and we are accustomed to look on nephritis as one of the common causes of oedema, but we should in reality be very hesitant in adopting such a view. The time has certainly not yet come when any man can claim to understand with full clarity the mechanism of oedema, but if the existing data are carefully and logically examined the balance of evidence to-day is against oedema ever being the direct consequence of disease of the kidney, though it is possible that the cause of the oedema may also provoke disease of the kidney.

The Views of Bright.

It is probably accurate to say that Bright's most famous work directed the attention of the world to the association between albuminuria, oedema, and disease of the kidneys, and it is perhaps an excessive piety which has made many of his successors cling to the notion that such oedema is a

necessary consequence of nephritis. I say an excessive piety because examination of Bright's actual words reveals the same dislike for dogmatism regarding this problem that we find in his expressed opinion on so many subjects. In his Goulstonian lectures he said:

'My conviction is complete as to the existence of some decided connexion between the three facts—anasarca, coagulable urine, and diseased function going on to diseased structure of the kidney. How these facts are connected or what necessary dependence the one may have upon the other, it is indeed difficult to point out, and some might suppose that we are rather perverting the order of events when we speak of the condition of the kidneys as causing anasarca';

but it is clear from the succeeding lines that his own opinion was in favour of the theory that oedema in nephritis is due to the disease of the kidneys.

If we follow the life-work of another great pioneer of internal medicine, Claude Bernard, we cannot fail to be impressed by the fact that his conviction that the mystery of diabetes mellitus was to be solved by a fuller understanding of hepatic disturbance not only wasted months of his own time, but led to many of his countrymen subsequently wasting years through too pious a belief in the infallibility of the master. The more carefully we read the works of Bright, the more must we be impressed by his caution in avoiding dogmatism; nor must we fail to note that occasionally, when dogmatic, he was wrong. Professor W. S. Thayer, of Baltimore, in an inspiring oration delivered last year at Guy's Hospital, recalled to his audience the fact, for example, that Bright stated that chorea was often the result of pericarditis. But on the question of the oedema seen in nephritis Bright was more cautious, and though he formulated his personal opinion he did so with reserve.

The Main Syndromes of Nephritis.

It is now common knowledge that when cases of nephritis are examined from the clinical point of view there are many

which stand out clearly owing to the presence of certain main features and a corresponding absence of other signs and symptoms. In the previous chapter I selected a case of cystic disease as illustrating in this manner uraemia without oedema. It is not more difficult to find cases where oedema and albuminuria are similarly conspicuous and uraemia and nitrogen retention absent. In Table X are set out the main

TABLE X

Marked	Albuminuria	Slight
,,	Oedema	Absent
Absent	Cardiac hypertrophy and hypertension	Marked
,,	Nitrogen retention	,,
,,	Tendency to uraemia	,,
Normal	Urea in urine	Low concentration
Normal or diminished.	Amount of urine	Polyuria or suppression
Normal	Specific gravity of urine	Low

features of cases of renal disease, placing in the columns on either side the characteristics of the two extreme types which diverge from the main general picture. These contrasting types constitute the **hydropiginous** and **azotaemic** nephritis of French writers and are often referred to in British and American writings under similar titles. It is quite easy to secure examples of either class, but to explain how disease of the kidney can produce results so entirely divergent is excessively difficult.

An explanation was at last offered by the theory of Widal, who, working with Javal in the early days of the present century, put forward the hypothesis that nephritis might affect the kidney in such a manner as to interfere either: (*a*) with its power of excreting urea and kindred nitrogenous substances, or (*b*) with its power of eliminating salts of which

sodium chloride is the most important. Cases of albuminuria with oedema, of the type to which long custom in this country has given the name of 'chronic parenchymatous nephritis', were thus explained as being examples of a derangement of the capacity of the kidneys to excrete sodium chloride without interference with the excretion of urea and other nitrogenous bodies.

The Theory of Salt Retention.

This view, which I gather from a very recent article by Lemierre to be still current, is founded chiefly on the fact that the administration of salt to patients with so-called renal oedema is followed by an increase in the oedema and a failure of the salt to appear in the urine. And the successful reduction of oedema by means of salt-free diets in some cases is held to be strong confirmation of the theory. But if the salt retention is due to failure on the part of the kidney, we should find an increase in the blood chlorides, and this has never been demonstrated in these cases. Moreover, it is now generally agreed that diminished excretion of sodium chloride is even more marked in the case of diseases such as cardiac failure and lobar pneumonia, where the renal function is not interfered with. When one proceeds from this to point out that the same kidneys which at first secreted a urine poor in chlorides will a week later, when oedema is subsiding, secrete a urine containing abundant chlorides, it becomes increasingly probable that the retention of salt is due to some extra-renal cause, or that, in the striking phrase of Fishberg, there has been a **'pre-renal deviation'** of both water and chloride, or, in other words, that these substances have been diverted into the tissues without the kidneys having had an opportunity of excreting them.

We know to-day that salt-free diets are of uncertain utility in oedema, but that on the whole they are more likely to be effective in cases of cardiac failure than in cases of so-called nephritic oedema. The salt-retaining kidney must,

I fear, be dismissed as a myth so far as it may serve as an explanation of oedema, for, if there is any type of kidney which is capable of retaining salt, it is not that associated with oedema, but rather the kidney where extreme destruction has led first to nitrogen retention, and, last of all, to retention of bodies such as sodium chloride which are normally not greatly subjected to concentration in their passage from blood to urine. Table XI shows the degree of concen-

TABLE XI (*after Fishberg*).

Substance.	*Concentration in*		*No. of times concentrated.*	*In renal insufficiency.*
	Urine.	*Blood.*		
Urea . .	2,000	30	65	Increased.
Creatinin .	75	2	35	,,
Phosphate .	150	3	50	,,
Chloride .	500	350	1·5	Not increased.
Calcium .	15	10	1·5	,,

tration undergone by certain of the commoner substances in the urine as opposed to their state in the blood. A short study of the figures in the third column gives the clue to the problem as to why some constituents, such as urea and phosphates, are so notably increased in the blood of all patients with renal impairment of high degree, for it is surely natural that the greatest difference will be found in those substances which are normally most concentrated by the healthy kidney. But with the final stages of renal impairment, even these bodies which are concentrated but slightly by the normal kidney become affected, and then, as de Wesselow and others have shown, an increase in the chlorides of the blood becomes apparent and may be demonstrated by means of salt test-meals.

The most marked examples of such retention are found in mechanical obstruction. Braasch has recorded a case of

obstruction to both ureters where the blood chlorides reached the extreme figure of 1,500 mg. per 100 c.cm., and Fishberg has observed a case where the figures rose to 1,000 mg. In uraemia following nephritis the concentration of blood chlorides does not often approach such heights, but an increase above the normal is probably always present in the terminal stages. We must, on the other hand, note that in such cases with high concentration of chlorides in the blood oedema is often conspicuously absent. If now we summarize the facts concerning chloride retention in nephritis, we can draw three important conclusions:

1. That in cases of 'renal' oedema there may be evidence of accumulation of chlorides in the watery subcutaneous tissues, but there is no evidence of chloride retention in the blood.

2. That there are cases of renal disease in which retention of chlorides in the blood is present, but such cases do not as a rule exhibit oedema.

3. That it is, therefore, probable that the accumulation of chlorides in the oedema fluid is due to an extra-renal factor.

An Illustrative Case.

From these theoretical considerations it will now be well to turn to a particular case illustrative of so-called renal oedema, a case selected on account of the absence of nitrogen retention and cardio-vascular features.

The patient, a man aged 22, has been under my care during the last 18 months. His early history was of insignificant childish ailments—measles, chicken-pox, and whooping-cough having affected him, but all slightly. Five years ago he had a trivial attack of pleurisy, and three years ago was troubled with a transient skin eruption. In the summer before last, during a holiday at a time when his health appeared to be excellent, he observed one day after bathing that his abdomen and legs were swollen. A few weeks later he noticed this swelling in the face, and became troubled with a transient epigastric pain, accompanied after a few days by diarrhoea. He noticed nothing the matter with his urine.

In the autumn of 1926 he consulted me at the Middlesex Hospital, when he was suffering from an obvious oedema of the

legs and lumbar region, together with some puffiness of the face. Ascites was present, and there was evidence of bilateral hydrothorax. The blood-pressure was 140/90; the heart apparently normal. After two days in bed the blood-pressure was found to be 100/70. The optic fundi were quite normal, the urine had a specific gravity of 1,020, and contained large amounts of albumin, together with a few hyaline and granular casts, but no blood. The Wassermann reaction was negative, and analysis of the blood gave normal figures as regards nitrogenous constituents and chlorides.

He was admitted to the Middlesex Hospital under the care of my senior colleague, Dr. C. E. Lakin, and was put on a diet containing abundant protein and no fat. The urine was found to vary in volume between one-third and three-quarters of a litre per diem. The daily albumin loss amounted to as much as 10 g. or more. Repeated blood analyses confirmed the normal nitrogen figures. The sedimentation time of the red corpuscles was considerably diminished, and the basal metabolic rate was 19 per cent. below normal. The urea in the urine varied between 2 and 3 per cent., and, after the administration of 15 g. of urea, rose to just about 3, showing full concentrating power. In addition to the generous protein diet, he was given urea in doses of 60 g. or more daily, and in a few weeks the oedema of the legs, face, and lumbar region completely disappeared, although there remained evidence of slight ascites. The daily albumin loss remained high, but the patient felt quite well in himself throughout the treatment. He has been seen at regular intervals during the subsequent 12 months, and through his oedema has fluctuated and never entirely disappeared it has never reached a degree sufficient to make him abandon his work. The albuminuria has always been excessive. He has, from time to time, been given thyroid extract, and shows a marked tolerance for this substance, but I have been unable to observe any definite influence thereby exerted on his general state.

Nephrosis.

Cases of this type are, one gathers, typical of that group which it is now fashionable to describe under the title of 'nephrosis', a word apparently first suggested by Müller and since adopted very widely, especially in the United States by Epstein and others, and in Germany by Volhard and

Fahr, Munk, and their followers. The word is ambiguous, in itself it conveys no clear concept, and a study of the literature reveals that it is used with a different connotation by different writers. In a paper published in conjunction with E. C. Dodds and D. T. Davies last year, an endeavour was made to define the prevalent views on the subject. We wrote:

'According to the conception of Munk, all renal disease with oedema, apart from heart failure, should be classed as nephrosis, whilst cases with haematuria, uraemia, and cardio-vascular complications constitute true nephritis. When a waterlogged patient gets an attack of haematuria, and the blood-pressure rises and nitrogen retention appears, it is nephritis complicating nephrosis; when, on the other hand, a patient after a febrile haematuria with transient hyperpiesis passes into a condition of anasarca, that is nephrosis supervening upon nephritis. It must be noted that in contrast to these views many British pathologists hold that the aetiology of all kidney disease is toxic, degeneration being always the first effect and reaction a later, but not inevitable, consequence, and that degeneration is itself an inflammatory phenomenon, whether followed by reaction or not.'

It may be added that a recent essay by such an authority as Professor Ludwig Aschoff confirms what I have quoted as being a correct interpretation of the German view. He writes:

'The meaning of this word has given rise to many differences of opinion in the past decades. . . . We understand it to mean those diseases of the kidneys which are characterized chiefly by degenerative changes of the tubular apparatus,' and later, 'the characteristics of Volhard's nephrosis, in the strict sense, are marked oedema and the excretion of much albumin in the urine, absence of the least increase of blood-pressure, and, therefore, also of the slightest hypertrophy of the heart.'

The case described above may, therefore, be accepted as a typical example of nephrosis, and it is further typical of this group in that the patient exhibits the lipaemia which is characteristic of all cases of pure nephrosis, and present in the vast majority of examples of 'renal' oedema of all classes.

Biochemical Aspects of Nephrosis.

The biochemical investigation of cases such as the above yields results which are largely negative: (*a*) The total daily volume of the urine is somewhat reduced when observed over any long period, but its urea-content is high during periods when one would expect it to be high. The specific gravity is consequently normal in its variations. Blood is absent, and the only casts are hyaline or granular. The notably abnormal constituents are albumin and certain lipoid substances which can be recognized by their doubly refractive properties when the centrifuged urine is examined by a microscope fitted with a polariscope. (*b*) The blood is normal as regards the nitrogenous substances and salts in solution, but abnormal in that it almost invariably contains an excessive amount of cholesterol. Examination of the blood proteins shows that the normal proportion of albumin to globulin is reversed. (*c*) The basal metabolic rate is usually considerably lower than normal.

Of these various findings the most striking is excessive cholesterol in the blood, which is incidentally almost certainly the explanation of the doubly refractive lipoids found in the urine. In Table XII are given the results of the estimation of cholesterol in the blood of the patient at different periods. It will be observed that they are almost invariably high when compared with the normal.

TABLE XII

Date.	*Blood-urea.*	*Blood cholesterol.*	*Oedema.*
October, 1926 . .	—	209	—
November, 1926 .	20	246	—
December, 1926 .	19	294	Better
February, 1927 .	26	117	—
March, 1927 . .	23	348	Worse
April, 1927 . .	29	528	Better
December, 1927 .	79	188	Much better
March, 1928 . .	75	244	No oedema

The subject of the blood cholesterol in nephritis has recently been carefully investigated by J. Maxwell in a large series of cases at St. Bartholomew's Hospital. He confirms the results of the numerous observers which Dodds, Davies, and I summarized in the communication already referred to. Maxwell found that an increase in the plasma-cholesterol is almost invariably associated with every type of renal oedema, and that though in chronic cases the actual height of the cholesterol figures is not necessarily proportional to the degree of oedema, its presence is evidence that the case will run a chronic course. He further concludes that renal oedema and the increased plasma-cholesterol are not related as cause and effect, but that both are probably the result of some toxic disease acting upon the cells of the reticulo-endothelial system.

As regards the reduced basal metabolic rate in cases of pure nephrosis, this factor has been stressed by Epstein, to whom we owe in such a large measure our knowledge of this group of cases. I have not personally experienced the success from the use of thyroid extract which he has claimed, and a good point of criticism is made by Murphy and Warfield, who point out that the water retention in the tissues of these patients gives them an illusive weight which renders estimation of the basal metabolism very difficult.[1]

Pathological Aspects of Nephrosis.

It is not easy to speak with exactitude concerning the morbid anatomy of cases of lipoid nephrosis for the simple reason that they are seldom fatal, but run a very chronic

[1] The patient described above was demonstrated at my Goulstonian lecture as a presumed case of pure lipoid nephrosis. It was stated at the time that though there was no sign of cardio-vascular disease, the recent blood analyses had shown an increase in the nitrogen-content of the blood. Three months later he died of uraemia in the Middlesex Hospital. At the post-mortem there was found slight cardiac hypertrophy, the kidneys were slightly but definitely contracted, and microscopic changes were present both in the tubules and in the glomeruli. The case, therefore, does not correspond strictly to pure lipoid nephrosis and can perhaps be said to illustrate the relative rarity of that condition.

course. It is indeed doubtful whether death ever occurs except as the result of some complicating or intercurrent disease. It is in this respect worthy of note that the termination is not infrequently due to a form of chronic peritonitis, possibly of pneumococcal origin, and perhaps due to accidental infection of the ascitic fluid. Cases of this type were included in a series reported by Dyke and have frequently been referred to by German authorities. When the kidneys of such a patient are secured, they are found to contain enormous quantities of cholesterol in the cells of the tubules and have the typical greasy appearance which has led to their being designated 'myelin' kidneys. This condition was first described in 1902 by Kaiserling and Orgler, and examples have been demonstrated by McNee and others in this country.

The histological characteristics of such kidneys are: (*a*) degenerative changes, usually confined to the tubules where the cholesterol esters are found in great profusion; (*b*) glomerular tissues little, if at all, damaged.

Rarity of Pure Lipoid Nephrosis.

The number of cases in which it is possible to speak of a pure lipoid nephrosis is certainly limited. Elwyn, who has made important contributions to this subject, believes that in all cases there is an initial glomerulo-nephritis which often heals, leaving tubal damage which has resulted from the absorption of the pathological glomerular transudate. Against this view must be put that of Murphy and Warfield, who have actually been able to demonstrate the kidneys of a case in which not the slightest evidence of a glomerular lesion could be found. In cases such as the one described I find no evidence that there was an initial lesion affecting the glomeruli, and the opinion of Epstein and of the German physicians is also to this effect.

But we may, on the other hand, accept the possibility of a primary pure nephrosis, without suggesting that such a

kidney may not easily undergo secondary damage of greater degree. An organ which is choked with cholesterol should from that fact alone be more readily susceptible to damage than is a normal organ. Or, if we examine the prognosis of such cases from the point of view of the possible effects of the prolonged hypercholesterolaemia, it is not necessary to suggest that such a blood condition is the result of renal damage, there is, indeed, no evidence for such a view, nor must it be assumed that the excess of blood cholesterol will produce a nephritis; we know, on the contrary, that patients with diabetes, or jaundice, or xanthoma may have hypercholesterolaemia for years without signs of kidney damage. We do know, on the other hand, that arterial lesions such as atheroma can readily be produced by cholesterol-feeding in animals; Scarff, in a recent series of experiments, has fully confirmed previous observations to this effect, and the work of Labbé and Heitz tends to show that the hypercholesterolaemia of chronic diabetes may be accompanied by such vascular changes that a very adverse effect on the general circulation, including the blood-supply to the kidneys, is to be expected.

There are, therefore, several reasons why cases of apparently pure lipoid nephrosis may subsequently develop signs of renal failure, and such a development is by no means incompatible with a primary condition in which these features were completely absent. In the case above described, for example, there appears during the last six months to have been a certain evolution which is perhaps ominous. The blood-urea and non-protein nitrogen have risen from their original normal level to figures which approach the low limits of the pathological. In addition to this, there seems to be a very slight, but definite, progressive elevation in the blood-pressure, and if continued observation confirms these findings we must conclude that there is progressive change going on in the kidney. But even accepting such a development as the fate of a number of these cases, there

remains a proportion in whom such an evolution never occurs, and we may draw certain conclusions from them, namely:

1. That the only strong evidence of nephritis presented by them is albuminuria.
2. That the balance of evidence is against the hypercholesterolaemia being an effect of renal damage.
3. That it is difficult to harmonize the localized histological changes in the kidneys of these cases with the theory that this is a true primary renal disease.

Is Oedema the Result of Albuminuria?

Returning now to the problem of oedema, the question at once arises whether either the hypercholesterolaemia or the albumin-loss found in lipoid nephrosis will furnish the explanation of the oedema so conspicuous in these cases. As regards cholesterol, it has already been pointed out that it does not appear to be the result of a renal lesion, but is rather the cause of the main renal abnormality. And when we inquire what relation it may have to the oedema, we are faced with two facts: (1) that in cases of hypercholesterolaemia due to jaundice or diabetes, there is usually no oedema, and (2) that, as Maxwell has shown, the cholesterol in 'nephritis' does not vary in proportion to the oedema, and, therefore, these two features can scarcely be cause and effect.

When we examine the possible relation between the oedema and the albuminuria, we become concerned with the views of Epstein, whose work on lipoid nephrosis must rank as one of the great advances of recent years. For not only was this observer the first to describe fully the features characteristic of this disorder, but we owe very largely to him our present knowledge that high protein feeding is desirable in its treatment. Epstein's views are further remarkable in that he is almost alone in having put forward a plausible theory to explain oedema as a direct effect of a renal lesion. His view is that the continued albuminuria causes such a depletion of albumin from the blood-plasma that the normal proportion

of albumin to globulin is eventually reversed. This brings about a lowering of the osmotic pressure in the circulating blood, and there is a consequent passage of water from the circulation to the tissues where the osmotic pressure is higher. Epstein's diet was specially chosen in an endeavour to replace as far as possible the albumin depletion by means of a generous supply of appropriate proteins in the food, and the frequent success of this diet lends apparent support to his theory of the mechanism of oedema. But in spite of its attractiveness this hypothesis has failed to convince the majority of the physiologists interested in the subject. It is clearly not possible to utilize such a theory to explain those types of oedema which follow starvation or faulty diet, or the oedema produced in inflammation and other pathological conditions, apart from circulatory failure, and it is perhaps on this account that the theory has found so little favour with the physiological school above referred to. Further, it is apparently difficult on the basis of this theory to explain the actual chemical composition of the oedema fluid; on the other hand, consideration of the writings of the pure physiological and pathological schools inclines one to the belief that they have perhaps not recognized the close association always encountered in clinical work in renal cases which exhibit both oedema and albuminuria.

When cases with cardiac oedema are carefully excluded, it is certainly very difficult to find a case of so-called renal oedema in which albuminuria is not a very marked feature, but close inquiry amongst cases of nephritis in pregnancy and acute glomerulo-nephritis always leads to the discovery of an appreciable proportion of cases in whom the oedema is out of all proportion to the daily amount of albumin lost. If, on the other hand, we examine cases of pure lipoid nephrosis, it will be found that albuminuria may persist with a very high total daily loss of albumin at a time when the oedema is rapidly disappearing or almost absent, and if the theory of blood depletion and lower osmotic pressure were the

explanation of the oedema, this should not be so. We are, therefore, once more confronted with an *impasse*, and must face the fact that the albuminuria, which is the one great index of a renal disturbance in cases of lipoid nephrosis, does not, on existing evidence, explain the oedema in these cases.

Certain Phenomena of Diuresis.

Some further information relevant to our problem can be obtained by examining various methods by which diuresis can be promoted in these cases. For once polyuria can be established the oedema subsides, and the mechanism by which polyuria can be provoked should therefore throw indirect light on the mechanism by which the oedema is governed.

Of the diuretics which often act successfully in 'renal' oedema there are at least three groups, which may be classed as follows: (*a*) urea and its precursors; (*b*) alkalis; and (*c*) acid-producing salts. In the first group must probably be included the high protein diets, and in the case described, urea in large doses was responsible for a rapid diuresis and reduction in the oedema.

In sharp contrast to this method must be placed that in which alkalis are employed. No discussion of oedema can in any way be complete without some reference to the school of thought which holds that acidosis is an important, if not an invariable, feature of oedema. M. H. Fischer may be quoted as one of the chief exponents of this view. His theory is largely based on experiments on frogs, and with colloidal substances such as gelatin. He believes that it is essentially the swelling of the tissue colloids under the influence of acid which is the main source of oedema in all cases. It would be impossible in the course of a single lecture to discuss the interesting views of this worker, which are frequently expressed in the vigorous language of an iconoclast. Fischer believes that alkalis are the essential basis for successful treatment in practically all cases of oedema and of nephritis,

and very similar views, perhaps characterized by an equal enthusiasm, are to be found in the work of Osman in this country.

The advocates of alkalis—and I may claim to be numbered amongst them—have apparently never been lacking in enthusiasm, for I have been interested recently to read a seventeenth-century work by Dr. William Coward, who was so enraged by the presumption of certain authors who had dared to belaud the use of acids in medicine that he published a volume entitled *Alcali Vindicatum*, or, 'The Acid Opiniator not guilty of Truth', in which his enthusiasm for alkalis led him so far as to cover with contempt a rival who had backed his favourable opinion of acids by the statement that 'Seamen and Surgeons had been cured of the Scurvy by eating Oranges and Lemons in Spain', after their return. Ignorant both of the action of vitamins and of the effect of citrates on the reaction of the urine, Dr. Coward in an outburst of sarcasm wrote, 'I love a Man who to make good his Cause tells half a Story and draws an Argument from a Tarpaulin to uphold a main point in Physick'.

Reverting to the use of alkalis in nephritis, we must recognize that diuresis can frequently be induced by their use if the administration is pushed to a sufficient degree. Osman gives as much as grs. 1,000 or grs. 2,000 of alkali, in the form of potassium citrate, potassium bicarbonate, sodium citrate, and sodium bicarbonate, to many of his cases, and in spite of certain alarming accidents in the nature of tetany, it appears that his method has not infrequently been successful in cases of mixed nephritis of desperate character. On the other hand, we must not ignore the fact that diuresis in similarly desperate cases has sometimes been achieved by the use of calcium chloride. Blum and the Strasbourg school are chiefly responsible for this work. When calcium excretion is thus promoted, the sodium content of the urine increases also, as shown by Keith, Barrier, and Whelan, but the most interesting fact from the point of view of our immediate inquiry is

that Salvesen and others have established that such calcium administration not only increases the urinary acidity but may actually cause a severe acidosis. We are, therefore, faced with the paradox that diuresis and improvement in the oedema of nephritis cases can apparently be brought about either by substances which render the urine alkaline, or by others which render the urine acid.

A possible explanation of this is afforded by the work of Stieglitz, who by means of indicator dyes has brought forward evidence that the reaction of the actual cells of the kidney is always the opposite of the reaction of the urine. And the same worker contends that any measure which tends to change the normal titre of the renal blood will act as a stimulus to the renal cells, and hence tend to produce diuresis. We must further note that following the work of Nash and Benedict there has been a tendency amongst biochemists to regard the breakdown of amino-acids into ammonia, which is one of the main protective mechanisms against excessive acidity of the blood, as brought about by the agency of the kidney, and not, as was formerly believed, by the liver. It is still too soon for any one to draw final conclusions from this mass of complicated observation, but it would seem to point to the conclusion that the work of the kidney in cases of oedema is directed to compensating an existing derangement of the normal blood chemistry, and though the strain of such compensation may damage the kidney the primary pathological process is an extra-renal one.

Experimental Oedema.

Turning now to the field of animal experiment, we find a series of failures which in sum seems to me to provide strong presumptive evidence against the theory that oedema is the result of damage to the kidneys. For so far as extirpation experiments are concerned, no one has succeeded in producing oedema by any operation on the kidney, and when we turn to the various poisons which on intravenous injection

cause a chemical nephritis, we find that with a single exception none of them can produce oedema. The exception is uranium, and it appears that in animals poisoned by uranium a chemical nephritis and oedema can be produced if the water-intake is forcibly increased simultaneously. I have seen it stated that the oedema of uranium poisoning occurs even when the animals' kidneys have previously been removed; but as I have failed to find corroboration of the statement, I do not wish to stress it. It is not unfair, however, to point to the grossly artificial nature of these experiments, which must surely produce toxic effects on extra-renal tissues which may alone be sufficient to cause oedema, and that such is the case is the conclusion reached by many of those who have had most experience with this type of experimental work. It is impossible to read descriptions of these experiments, such as that to be found in the monograph of Loeb, without being impressed by the dissimilarity between such experimental oedema and that seen in pure lipoid nephrosis. And this work as a whole seems to me to support rather than challenge the belief that 'renal' oedema is of extra-renal origin. The same conclusion is reached if we examine the interesting experiments recently devised by Aldrich and his associates, who have made prolonged study of the rate at which salt solution disappears after it has been injected into the skin of patients with various types of oedema. Without entering into details of their findings, it may be said that even in cases of so-called renal oedema they have found strong evidence of an abnormal avidity for water on the part of the tissues, both during and before the occurrence of the actual oedema.

Theories of Oedema.

Throughout this chapter I have made no attempt to explain the mechanisms by which the passage of fluid into the tissues, which we speak about as oedema, may be produced. No one who has given more than superficial attention to the

enormous amount of work which has been done on this subject would presume to support any existing explanation of the facts with anything other than diffidence. Well-known treatises on the subject, such as the monograph by Loeb, or the work of Martin Fischer, tend to leave the reader in a state of confusion as great as that in which he may have begun his study of the subject, and we are forced to the conclusion that there is no theory of oedema before the medical world to-day which will explain all the known facts, but the theories which depend on the hypothesis that the oedema is a direct consequence of renal injury break down almost from the onset.

Elwyn, who must be quoted amongst those who have given particular attention to this subject, finds it impossible to do more than summarize existing facts, and put forward a tentative hypothesis to the effect that the oedema is a compensatory process. He believes that amongst the physiological constants of the body the blood-volume is an important one —i.e. that in all circumstances, if life is to be maintained, the volume of the blood must remain constant. In cases of 'renal' oedema, and of lipoid nephrosis as an outstanding example of such cases, he believes that reduction in urinary volume is the first compensatory mechanism to be brought into play and is directed to arrest the loss of albumin in the urine. From this he goes on to the belief that when this first great gateway of escape for the fluids from the circulation is partially closed, an increase in the blood-volume would necessarily occur if some other gateway were not open. The only other avenue of escape for the fluid is into the tissues and thither it proceeds. This theory, as its author frankly says, is merely a statement of certain regulating mechanisms, and offers no explanation of the mechanisms by which the oliguria is produced or the transudation into the tissues brought about. Acceptance of it would seem to imply a change in the permeability of capillaries throughout the tissues, or, in other words, the existence of an extra-renal

factor as a main factor in the production of so-called renal oedema.

General Conclusion.

I have now set out the main reasons for my belief that *oedema in nephritis is at once suggestive of pathological change in tissues other than the kidney, and that such pathological change is not the result of nephritis, although it is more than probable that the renal and extra-renal damage have a common cause.* If this view is accepted, it seems to call for a fundamental change in our conception of the nature of nephritis, whenever that term is employed to describe a clinical association of oedema and albuminuria with or without haematuria, nitrogen retention, and cardio-vascular changes. No one to-day would dream of regarding a case of acholuric jaundice, or of myelogenous leukaemia, as an example of splenic disease, and similarly I feel that the time has come when we must, at any rate in all cases where oedema is prominent, direct our attention first to the extra-renal tissues and search there for the factor that is the cause of pathological change of a very wide nature.

CHAPTER IV

THE PROBLEM OF BLOOD-PRESSURE IN NEPHRITIS

In Chapter II was described a case in which the patient died of uraemia following progressive destruction of both kidneys by cystic disease. This case was selected in order, first, that the problem of uraemia might be studied in a case of non-inflammatory destruction of the renal substance, and, secondly, because neither oedema nor elevation of the blood-pressure was a marked feature of the case. In other words, the case illustrated the important fact that uraemia is not necessarily associated either with renal inflammation, or with so-called 'renal' oedema, or with hyperpiesia.

In the following chapter I endeavoured to summarize the evidence by which one is driven to the conclusion that oedema occurring in cases of renal disease points to tissues other than the kidneys being affected, whilst there is no evidence to prove that such oedema is the result of the renal lesion.

I now approach the subject of high blood-pressure, and am at once aware that the problems here are even more difficult than those already discussed. For in the case of uraemia and oedema we are confronted with masses of complex data the sifting of which is a task of great difficulty, although certain conclusions emerge after close analysis. When considering high blood-pressure and its relation to renal disease, on the other hand, one is often confronted with an absence of essential data which makes it impossible to draw conclusions at all.

The patient whose story was discussed in Chapter II, and the man described in the following chapter, illustrate the frequency with which hyperpiesis is absent in cases of renal disease. We can perhaps best approach the subject by first inquiring into the groups in whom hyperpiesis is most marked. There are at least three of these:

(A) That which constitutes what has too often been called 'chronic interstitial nephritis' or 'granular kidney'.

(B) The group which embraces the renal complications of pregnancy, including eclampsia.

(C) The acute glomerulo-nephritis which is seen as a complication of scarlatina and some other infectious diseases.

It will be well to examine these groups in greater detail.

'Chronic Interstitial Nephritis'; Essential Hypertension.

Of all cases with renal disease those in this group probably exhibit high blood-pressure most prominently. They were well recognized by Bright, who in his Goulstonian lectures spoke as follows:

'In April, 1830, Dr. George Burrows brought me a kidney in a most confirmed state of granulation, so completely pervaded with deposit as to have lost all the structure of the cortical portion, and to have put on a marked scabrous wall externally. This was taken from a patient who had been in St. Bartholomew's Hospital for a fortnight only with confirmed anasarca, and in addition to the disease of the kidney, the heart was greatly enlarged and otherwise diseased. In this case . . . the urine had shown no tendency to coagulate by heat.'

He goes on to quote a still more interesting case brought to his observation by Dr. Watson of the Middlesex Hospital—

'the kidneys showed the typical organic change found in anasarcous patients which is so often accompanied by the secretion of albuminous urine, but this state of the urine did not exist during the time he was under Dr. Watson's observation, and the action of the kidney was so far annihilated that even by gin and stimulating diuretics only a scanty secretion was obtained',

and in a later paragraph he records the important fact that the heart was much enlarged without any sufficient cause being found. Elsewhere in the same lectures Bright several times remarked on this mysterious association of cardiac hypertrophy and sclerotic kidneys and on the irregularity of albuminuria in such cases.

It should be unnecessary to state that these cases were the

subject of the classical studies of Gull and Sutton, who under the name of arterio-capillary fibrosis described the generalized change in the small vessels which is now usually considered the primary cause of the renal changes.

To another physician at Guy's Hospital, Dr. F. A. Mahommed, we owe the continuation of this work and almost the earliest observations on the blood-pressure in such cases. He clearly paved the way to the work of Sir Clifford Allbutt and others, who have shown convincingly that IN AN ENORMOUS NUMBER OF CASES OF CONTRACTED KIDNEY THERE IS EVIDENCE OF HIGH BLOOD-PRESSURE FOR MANY YEARS BEFORE ANY RENAL LESION MAKES ITSELF MANIFEST. The work of these observers has been well described in a recent article by Ryle.

'Hyperpiesia', 'essential hypertension', and '*arteriolosclerosis*' are synonyms used in the description of this condition, which formed the subject of one of the Goulstonian lectures delivered by Dr. Geoffrey Evans six years ago. Its aetiology remains obscure; it is probable that the high blood-pressure is at first the result of a widely distributed spasm of the arterioles, and that the anatomical change which Evans describes as 'diffuse hyperplastic sclerosis' is a subsequent event. Moreover, the physiological researches of Anrep and Starling, and the pathological investigations of Bordley and Baker, produce evidence that the failing blood-supply to the medulla oblongata is of primary importance in the genesis of these vasomotor responses which establish the condition of prolonged hypertension.

Whatever will in the future be established as the explanation of this disease, the present evidence is against the probability that the renal changes are either of primary importance or of invariable occurrence. Fishberg in an investigation of seventy-two of these cases found advanced renal disease present in only five at autopsy, and his conclusion that the anatomical changes of the kidney are not compatible with the theory that hypertension is primarily due to a

disorder of the renal function is one which finds increasing acceptance at the present day.

We must recognize that there are at least three stages in the development of this disease if we include only those cases which at some time exhibit evidence of renal disease. There are probably many patients in whom the kidney escapes damage altogether. But taking the evolution of a case which terminates in uraemia, following progressive destruction of the renal substance, the patient will exhibit—

1. A stage in which there is hyperpiesis, with a systolic pressure in the neighbourhood of 200, left-sided ventricular hypertrophy, and probably no other sign or symptom for many years. The effects of such an abnormality may lead to cardiac failure or cerebral haemorrhage, but these complications are outside our present survey and we will confine our attention to those cases in which the kidney suffers.

This being so, our patient will pass on to—

2. A stage in which the progressive disease of the arterioles in the renal tissues is beginning to reduce the areas of effective kidney substance to a pathological degree. The patient's condition is now similar to that of an animal in which more than half, but less than three-quarters, of the renal substance has been extirpated. The number of functioning glomeruli and tubules is so reduced that the kidney cannot excrete its full quota of urea in fully concentrated form, but it is able to do so provided that such urea can escape in a dilute condition. There are, accordingly, no changes in the blood chemistry but a polyuria is present, and by day and by night the patient passes large quantities of urine of low specific gravity containing a low concentration of urea. This is what Fishberg has designated 'compensated renal failure'.

From this stage the patient gradually passes on to—

3. A stage in which he cannot excrete all the waste products of protein metabolism, even in a dilute condition. He therefore continues to exhibit a urine of low specific gravity and fails to respond to tests such as the urea-concentration test. But, in addition, he has an increasing retention of nitrogenous substances in the blood, and this nitrogen retention becomes more and more marked, is accompanied by phosphate retention, and finally by

a retention of substances such as chloride which normally exhibit but little concentration during their passage from blood to urine. He dies in uraemia, and at the autopsy small red contracted kidneys are found.

These, then, are typical examples of arterial hypertension with renal disease, and they are to be regarded as cases in which a progressive narrowing of the arterioles has produced secondary disease of the kidney, and the following conclusions emerge:

1. On available evidence we must believe that 'chronic interstitial nephritis' so called and essential hypertension are different stages of one and the same disease.

2. In this disease hypertension always precedes, often by many years, all clinical signs of renal damage. In the later phases hypertension is found associated with all grades of renal insufficiency.

3. The anatomical change found post mortem in this disease consists of: (*a*) a generalized sclerosis of the arterioles; (*b*) cardio-vascular hypertrophy; (*c*) varying degrees of ischaemic destruction of the renal tissues.

4. Renal sclerosis is part of a generalized vascular change, and is in all probability neither an early nor even an essential part of this vascular change.

5. Hypertension and diffuse sclerosis of the arterioles must be considered as associated manifestations of a single disease, though at present we are unable to prove that hypertension is either the cause or the effect of these vascular changes.

The Renal Complications of Pregnancy.

In discussing this branch of our subject we are again confronted with difficulties of nomenclature. During pregnancy a series of complications is frequently encountered, ranging from the appearance of a slight albuminuria with no other sign or symptom, to severe albuminuria, oedema, marked elevation of blood-pressure, and generalized convulsions. Cases with convulsions are almost invariably labelled as

eclampsia, and though it is well recognized that oedema may be absent in such cases, eclampsia can never occur without some of the phenomena—albuminuria, oedema, or hypertension—which are usually accepted as placing a case in the category of renal disease.

It has often been suggested that eclampsia is merely uraemia occurring in the course of a complicated pregnancy, and if we accept the thesis that uraemia is a term covering several different conditions, there seems no sufficient ground for excluding eclampsia from the definition. It is, at any rate, sure that *eclampsia is merely a name given by obstetricians to a clinical syndrome in which certain manifestations due to a renal disorder, and severe generalized convulsions, make their appearance at some time close to the moment of parturition.*

Certain observers, such as Lubarsch and Fahr, and more recently Berkeley, Dodds, and Walker, have held that eclampsia differs from ordinary renal disease in that there is an important element of hepatic disorder always present, but though it is accepted that many eclamptic cases give evidence of a disturbance of the liver, the recent observations of Cruickshank, Hewitt, and Couper on sixty-nine cases suggest that such signs of hepatic disturbances are relatively uncommon in this syndrome.

Whether cases exhibiting jaundice or other signs of hepatic disorder can properly be included under the heading of eclampsia, or whether, on the contrary, the term eclampsia should be reserved solely for such cases, it seems abundantly clear that at the present date we must continue to class together all the cases in which convulsions are combined with certain renal signs during the period of parturition, and when for the purpose of our present inquiry we ask what the relation of this state is to increased blood-pressure, we must accept it as established that an elevation of the blood-pressure is almost invariably present.

Examination of a large series of cases, such as that of Cruickshank and his co-workers, shows that this increase in

blood-pressure is not usually excessive, the systolic pressure being generally in the region of 160 mm., reaching 200 in perhaps 20 per cent. of cases, and being below 140 in a further 20 per cent. In general it appears to be established that the prognosis becomes worse in cases where hypertension is most marked. When these cases are examined after parturition it is found that in the majority of them the blood-pressure quickly falls to normal, but the elevation may persist or even increase, and I have attending my out-patients at the Middlesex Hospital several patients in whom hyperpiesis has persisted for years after this complication of pregnancy.

Turning now to the renal complications of pregnancy in which convulsions do not occur, we may first of all exclude a large group in whom the presence of albumin in small amounts in the urine is the sole evidence of any abnormality, but having done this there remains a very numerous class in which albuminuria is accompanied by oedema in varying degree, often with headache or vomiting or cerebral symptoms indicative of a severe general disturbance. It has become customary to classify some of these cases as 'pre-eclamptic toxaemia' and others as 'nephritic toxaemia', but after prolonged and careful investigation of many of such cases, and a study of the literature dealing with them, I have never been able to discover any logical means by which an individual case can be placed in one or other of these groups. It rather appears that the method adopted is for the surgeon in charge of the case to call a case pre-eclamptic toxaemia when he has the impression that without treatment convulsions would have occurred, and to class it as nephritic toxaemia if a history of scarlet fever or the appearance of blood and casts in the urine, or some other manifestation, gives him the impression that the strain of the disease has fallen with particular acuity upon the kidney. In the same way it must be agreed that in series into which prolonged investigation has been made, such as that incorporated in

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the report to the Medical Research Council to which reference is made above, one often finds classified as simple albuminuria cases in which oedema and sometimes a definite elevation of blood-pressure was present and which, therefore, would appear to fall more properly into one of the other groups. If we look upon these cases as a whole, we find that some elevation of the blood-pressure is present in the majority of them, if the cases where albuminuria is the only symptom are excluded, and in the group, which, to my mind for purely arbitrary reasons, has been labelled nephritic toxaemia the average blood-pressure is very little, if at all, lower than in those with eclampsia. Indeed, it may be said that examination of the reports on such cases leaves the impression that a high blood-pressure is one of the chief determining factors which lead to the inclusion of a case in the so-called 'nephritic' group.

One must conclude that a moderate degree of hypertension is found in a high proportion of these cases, also that though such elevation of the blood-pressure is frequently transient there is a definite residuum of cases in whom it persists for years afterwards, and possibly for ever.

But a far more important problem which arises at this point is this: Does the hypertension seen in the renal complications of pregnancy occur as a result of the complication, or was it present prior to the occurrence of any other symptom? To this all-important question I am unable to find a reply. I have the impression, and I think it is a general impression, that the hyperpiesia does not occur until albuminuria or some other evidence of renal involvement is present. But it is quite possible that it occurs at an earlier date, and it seems certain that in some proportion of these cases it was present even before pregnancy. We can draw no final conclusions from these cases until we are better informed concerning this point, and particularly it would seem that the answer to this question will supply us with the all-important information as to whether hyperpiesis persisting after preg-

nancy is the result of a renal complication of pregnancy or is to be regarded as a separate disease.

The Term 'Toxaemia of Pregnancy'.

Physicians owe a great debt to the obstetric surgeons and their assistants who have made such careful inquiry into these problems, even though they remain in many ways mysterious. It is, indeed, unquestionable that we already possess many data from these cases which we should be glad to have in the case of similar purely medical ailments, and there is much to be said in favour of the attitude which persists in classifying such cases as 'toxaemia of pregnancy', for that term tends to keep in view the general nature of the disease or diseases, in which clearly the renal manifestations are but a part of the whole.

The morbid anatomy of the 'pregnancy kidney' tends to show that the lesions present are of an almost purely degenerative character and the almost constant presence of oedema is—if the conclusions of the previous chapter are accepted—evidence of the coexistence of an important extra-renal factor. It is of interest in this connexion to note that Petersen and Lash have observed an increased permeability of the capillaries in pregnancy, pointing to an important extra-renal factor always present in this state.

It is not my intention here to enter into any discussion of the pathogenesis of the renal complications of pregnancy. It seems, indeed, far too soon to endeavour to draw any conclusions on this subject, but we should bear in mind that Volhard and other German workers believe that a general spastic contraction of the arterioles is the most important factor in the production of all the manifestations of such disease. Volhard believes that in eclampsia and in convulsive uraemia generally, there is an oedema of the brain due to contraction of the arterioles, that such oedema is followed by compression of the capillaries and cerebral anaemia, and that this is the cardinal cause of the fits.

Elwyn has suggested, following the ideas of Gaskell, that an increased irritability is physiologically present in the pregnant uterus, and that such increased irritability is part of a similar condition present throughout the vegetative nervous system, and that hence there is an increasing tendency to vasoconstriction throughout the course of pregnancy.

'The possibility for the occurrence of arterio-spastic contraction lasts as long as these mechanisms retain their increased irritability. This is probably until the uterus is completely involuted. For this reason eclampsia may still occur in the puerperium.

Looking back over this subject, the following conclusions may be drawn:

1. A moderate degree of hyperpiesis is found in about half the cases where pregnancy is complicated by albuminuria and oedema.

2. When eclamptic convulsions occur such hyperpiesis is present in a still larger proportion of cases.

3. The degree of hyperpiesis is some index of the severity of the case.

4. The raised blood-pressure does not persist in the majority of cases which recover.

5. There is insufficient evidence as to whether the hyperpiesis appears before or simultaneously with the albuminuria and oedema.

6. It is not possible to form an opinion as to whether the hyperpiesis is the cause or the effect of such renal lesions as occur.

Acute Glomerulo-nephritis.

We now come to acute nephritis of the type that occurs as a complication of scarlatina and other infections. There is to-day almost a consensus of opinion that such acute nephritis takes one of two forms: (*a*) that which is known as the **focal type,** in which the inflammation of the glomeruli is limited to a certain proportion of the total kidney substance;

and (*b*) a **diffuse type** in which all the glomeruli are uniformly involved with a varying degree of inflammation.

The former type is probably more frequently associated with diseases such as acute tonsillitis and pharyngitis, and is frequently characterized by a considerable degree of haematuria. Owing to the limitations of the amount of kidney substance involved, there is seldom any noticeable reduction in renal function, and the course of the disease tends to be benign. Oedema and hypertension are probably always absent.

In sharp contrast to this, the acute diffuse glomerulo-nephritis usually makes its appearance in the second or third week of an infectious fever, and, though the disease is of a far more serious character, haematuria is seldom marked, and streptococci, which are usually to be found readily in the urine of patients of the previous class, can seldom be demonstrated in this disease. It again contrasts with the focal type in that oedema is usually present to some degree, and in that an elevation of the blood-pressure is frequently remarked.

It is regrettable that precise data concerning our immediate problem are even more difficult to obtain in these conditions than in the case of the renal complications of pregnancy. This is probably due in a large measure to the fact that these cases are usually segregated in fever hospitals. One would imagine that this very fact might favour the acquisition of scientific information, but unhappily this is not so at present.

In any case, the information concerning the incidence of hyperpiesis in acute glomerulo-nephritis is to-day lamentably inadequate. Christian and O'Hare state that in only nineteen of fifty-five successive cases of this disease was there any increase in the systolic pressure, and in all cases in whom that pressure exceeded 180 or more they consider that a chronic nephritis had been present prior to the acute attack.

So far as it is possible to draw conclusions, one may perhaps say that:

1. A moderate degree of hyperpiesis is found in a small proportion of cases of acute diffuse nephritis; it is by no means an invariable feature.

2. Oedema is probably an accompaniment of all such cases.

3. The blood-pressure returns to normal in the majority after the subsidence of the acute attack.

4. Cases with a greater degree of hyperpiesis are probably those in which this condition was present prior to the acute attack, and in such cases high blood-pressure will persist.

Chronic Diffuse Glomerulo-nephritis.

When we consider the chronic state into which many of these cases of acute nephritis pass we enter into the most mysterious portion of the whole of the difficult subject of nephritis. There can be no question but that recurrent attacks of acute inflammation of the renal tissues are seen in an appreciable number of such cases, and it is usual for such attacks to be accompanied by oedema and for the degree of hypertension to increase with each successive attack. In the course of time a permanent reduction in renal function becomes apparent. Polyuria is present because the concentrating power of the kidney is lost, and from this the patient passes to a stage of uncompensated renal failure, when nitrogen retention in the blood is present.

In the course of this evolution it is usual for a progressive elevation of the blood-pressure to occur, but the figures seldom reach the height seen in the primary hyperpiesia which produces granular kidney as a terminal event. But although these cases of chronic glomerulo-nephritis usually exhibit progressive hypertension with cardiac hypertrophy, it must be recognized that there are certain rare exceptions. Thus Jores, Foster, Bouchet, and Bannick have all reported cases of well-marked chronic glomerular nephritis in which there was typical nitrogen retention, and, following death from uraemia, the kidneys were of typical fibrotic appear-

ance, although there had never been elevation of the blood-pressure during life and the heart was not enlarged.

We must conclude that:

1. In cases where diffuse glomerulo-nephritis becomes chronic there is usually a progressive elevation of the blood-pressure.

2. This hyperpiesis very seldom, if ever, reaches the high degree found in cases of 'essential hypertension' and is occasionally completely absent.

I have endeavoured in the diagram (Fig. 1) to set out the nature and incidence of hypertension in the common medical diseases affecting the kidney so far as one can form an opinion in the light of our present incomplete knowledge. For each main group I have drawn three columns of which the central one represents the blood-pressure when the case comes under observation as an example of 'nephritis', the columns in the left of this being the tension before this period and the right-hand column the subsequent finding. The relative breadth of each column shows roughly in what proportion of cases the blood-pressure is abnormally affected. Thus I have indicated that in acute diffuse nephritis a transient hyperpiesis, affecting a moderate proportion during the attack, becomes a permanent hyperpiesis in a few cases. In the toxaemias of pregnancy such cases probably include some who exhibited hypertension before ever their pregnancy occurred. In lipoid nephrosis, hyperpiesis is so rare as to make the accuracy of the original diagnosis doubtful when it is present, whilst in the group which is usually labelled chronic interstitial nephritis, the hyperpiesia long preceded the renal manifestations.

Can Renal Lesions Cause Hyperpiesis?

A question of paramount importance now presents itself. It is this: Have we evidence on which we can affirm that a renal lesion can by itself produce an elevation of the blood-pressure?

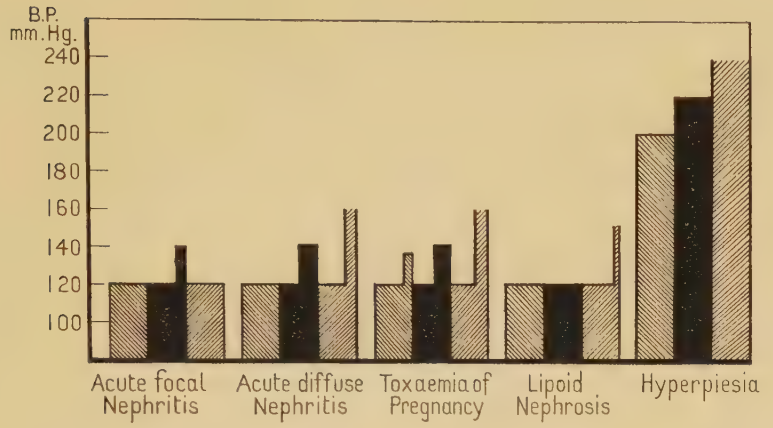

Fig. 1. Diagrammatic representation of changes in blood-pressure met with in nephritis

On physiological grounds one would expect the answer to be 'yes'. A certain pressure in the renal arterioles is a necessity if the glomerular filter is to remain effective, and when a number of glomeruli are incapacitated by disease an increased pressure would seem to be needed if the remainder are to carry on their work properly.

It must be borne in mind that, like other essential organs, the kidney possesses considerable powers of reserve. The classical experiments of Rose Bradford demonstrated that it was necessary to remove three-quarters of the total kidney substance before renal failure was established, and the repetition of these experiments by Janeway and others has tended to show that such successive reductions in the renal tissue are accompanied by a moderate elevation of the blood-pressure.

The question cannot be accepted as finally settled even to-day, for Anderson failed to produce hypertension by similar experiments on rabbits even when large amounts of the kidney substance had been removed, and permanent nitrogen retention with slow death had been produced. By giving high protein diets to such animals this observer was able to produce nitrogen retention even when so small an amount as 12 per cent. of the total kidney substance had been removed, but again there was no hypertension though extensive atheroma of the aorta was produced in many of the animals. We may perhaps assume that further evidence produced by ingenious experiments will finally demonstrate that destruction of sufficient renal tissue is followed by a rise in the blood-pressure; the balance of evidence is probably in this direction even to-day.

But even if this be the fact, we are still far from knowing the mechanisms by which such hyperpiesis is produced. I will not go into details concerning the many negative observations which characterize the chemical side of such investigations; suffice it to say that none of the nitrogenous constituents of the urine has been shown to increase the blood-pressure when present in excess in the blood, and many

hundreds of observations testify to the fact that such things as urea, uric acid, creatinin, chlorides, phosphates, and so on can exist in excess in the blood-stream for months or years without producing high blood-pressure.

Cholesterol has been the subject of particular inquiry in this respect, but it is now generally agreed that though atheroma and other degenerative changes in the arteries can be produced by cholesterol, excess of cholesterol in the blood is more characteristic of cases of lipoid nephrosis with a normal blood-pressure than of cases of renal failure with hypertension.

The search for a pressor substance in the kidney itself is a chapter in the history of medical investigation which so far is a tale of failure. Investigation, however, continues, and it seems likely that the future will demonstrate that hypertension in some degree can be a direct result of nephritis and renal disease. We must, however, recognize that the evidence points to such hypertension being only slight in degree and that when any patient exhibits an extreme degree of hyperpiesis, a systolic pressure, for example, in the region of 200 or higher, that fact is strong evidence for the existence of an extrarenal factor; and, indeed, in any such case the probability will be that such renal damage as may be present is the result and not the cause of the morbid vascular change to which the high blood-pressure is due.

The Need for a Wide Outlook.

It will be well to conclude this chapter by emphasizing the necessity of considering nephritis from a very broad point of view. Few organs in the body are exposed to so many influences of potentially dangerous character as is the kidney. It is perpetually exposed to attack from bacteria which may invade the blood-stream, or which may with equal danger reach it by the lymphatics or the ureter. It is also called upon to play an important part not only in the excretion of waste products from the blood, but in the adjustment of the proper

Fig. 2

Fig. 3

ALCOHOLISM IN THE DAYS OF BRIGHT
From a contemporary publication by George Cruikshank

balance between acid and alkali in the blood-stream, and one has only to examine the work of Nuzum or a score of other observers to realize how readily damage can be produced by chemical products from even normal food-stuffs when these are given in excess.

Dodds and Baker, working in the laboratories of the Middlesex Hospital, were, some years ago, able to establish the fact that an injection of haemoglobin in the blood-stream of a rabbit would produce fatal renal damage if the animal's urine was acid, but was innocuous when such urine was in an alkaline condition. Here again is an illustration of how apparently slight chemical factors may influence the pathology of the kidney.

L. S. Debenham, J. Joffe, and M. S. Pembrey demonstrated to what a striking degree the renal secretion can be affected by influences such as heat and cold directed to the skin surface of the body. So delicate is this response of the kidney to vasomotor changes in the capillaries of the skin that it is very probable that a so-called nephritis may accompany excessive stimuli or actual disease of very distant parts of the circulatory system.

The two pictures (Figs. 2 and 3) here shown may at first appear entirely irrelevant to our subject, but this is not so, for they reveal the conditions prevalent amongst the patients on whom Bright made his observations. The pictures are from George Cruikshank's famous series entitled 'The Bottle', and there can be little doubt that they express in dramatic but not exaggerated form the extent to which alcoholism prevailed in this country at that period. It seems not unlikely that this aetiological factor explains to some extent the differences shown in Bright's *Reports of Medical Cases* from the pictures of nephritis which we are accustomed to see at the present day. This impression is strengthened by reading the text of these reports, a typical example being that of—

'Henry Izod, a Smithfield drover, a man of very irregular habits who had long been accustomed to getting intoxicated with

porter, but had only taken spirits to excess for the last year, during which time he had generally lodged at a public-house and had been exposed in his work to the inclemency of the weather, seldom wearing a hat, never changing his clothes when wet, and being almost daily intoxicated.'

Surely it is not unnatural to suppose that a dietetic exuberance of this degree may have played an important part in the pathology of that epoch, and I make the suggestion to emphasize the breadth of the view we must take of all cases to which the narrow definition of nephritis is applied. For such chemical influences as may affect the kidney will also throw a load upon extrarenal tissues, and especially on those of the circulatory system, and I have tried to show how the study of uraemia involves inquiry into very broad biochemical principles, how oedema is probably always an index of damage to tissues outside the kidney, and how hyperpiesia is more often a cause than an effect of nephritis.

In a famous lecture Sir William Gull spoke as follows:

'It is always dangerous to rest under a narrow pathology; and I believe that it is a narrow pathology which is satisfied with what you now see before you on this table. In this glass you see a large hypertrophied heart and a very contracted kidney. This specimen is classical. It was, I believe, put up under Dr. Bright's own direction and with a view to showing that the wasting of the kidney is the cause of the thickening of the heart. I cannot but look upon it with veneration, but not with conviction. I think with all deference to so great an authority that the systemic capillaries, and, had it been possible, the entire man, should have been included in this vase, together with the heart and the kidneys, and then we should have had, I believe, a truer view of the causation of the cardiac hypertrophy and of the disease of the kidney.'

His words applied to cases of hyperpiesia with secondary destruction of the kidney, but the same broad outlook should be employed when regarding every type of renal disease.

CHAPTER V

THE CLASSIFICATION OF NEPHRITIS

THERE is much to be said in favour of calling diseases after their discoverers rather than by names which attempt to convey a scientific description of their nature. So often it happens that our knowledge is not yet exact or that the limitations of the language are so great that a supposedly scientific name becomes in reality either a mis-statement or a terminological abomination. Few pathologists will accept the word 'lymphadenoma' as a proper description of Hodgkin's Disease, 'lympho-granulomatosis' is an unwieldy word and may very likely prove to be inaccurate as a description, whilst 'Hodgkin's Disease' is a useful term both from the point of view of history and of euphony.

For somewhat similar reasons it would perhaps be an advantage if we employed the term 'Bright's Disease' instead of speaking about 'nephritis'. Nephritis implies that we are dealing with an inflammatory disease of the kidneys and, even accepting the hypothesis that degeneration alone, without regeneration, may constitute inflammation, it must be accepted, as I have been at pains to demonstrate in preceding chapters, that few, if any, of the conditions usually grouped together under the heading of nephritis can be looked upon as diseases of the renal tissues alone, and in many examples the pathological change in the kidney is of very minor degree when compared with that found elsewhere. It is for this reason that attempts at classification based on the morbid anatomy of the kidney as found in the post-mortem room fall almost invariably short of the mark.

Classifications based on a few cardinal symptoms with a main conception of a 'hydropiginous' and an 'azotaemic' type as described in Chapter III are equally unsatisfactory in that some, and perhaps the majority, of the cases encountered in practice fail to fall clearly into either group.

Preliminary Classification.

In the two preceding chapters I have endeavoured to show that it is possible to separate from the main welter of 'nephritis' two diseases which may usefully be taken as the two extremes between which all other categories of Bright's Disease must be included. At the one extreme is lipoid nephrosis, clinically distinguished by intense albuminuria and a massive anasarca, without the slightest sign of cardio-vascular change, arising insidiously, chronic but benign in course, exhibiting little chemical change in the blood save hypercholesterolaemia, and producing apparently no anatomical change in the kidney except a tubal degeneration which is in many cases a transient occurrence. The disease is probably of metabolic origin and its renal manifestations are not more than a trivial part of the picture.

At the other end of the scale is arteriolo-sclerosis, the 'arterio-capillary-fibrosis' of Gull and Sutton. This is believed to begin as a generalized spasm of the **arterioles,** producing, in its earlier stages, high blood-pressure alone with a compensatory hypertrophy of the heart. This disease may produce no demonstrable renal effects whatever, and it is only in a certain proportion of all cases that the kidney tissues suffer sufficiently for renal failure to become manifest. To classify such cases under the heading of 'chronic interstitial nephritis' would appear to be grossly unscientific.

Between these two extremes are to be found that large group of cases now usually referred to as 'glomerulo-nephritis' in which the pathologist can invariably demonstrate morbid changes in the kidney, such changes being due to bacteria or their toxins, and giving perhaps valid reason for regarding the kidney as the organ which has principally suffered in a disease which is blood-borne in its origin.

In glomerulo-nephritis, whether acute or chronic, both oedema and hypertension are almost invariably present at some time. In chronic cases hypertension is accompanied

by cardiac hypertrophy, although the cardio-vascular phenomena are seldom so prominent as they are in cases of primary arteriolo-sclerosis. Haematuria and casts of the renal epithelium are usually accompaniments of acute exacerbations and supply evidence of the active inflammatory process in which the kidney is involved. Uraemia is of fairly frequent occurrence during acute stages, and may occur as a final event in chronic cases where repeated inflammation has brought about permanent renal failure.

It is now recognized that glomerulo-nephritis may occur in several forms to which reference has been made on p. 53, and there is in addition an embolic type of glomerulo-nephritis which occurs in conjunction with sub-acute bacterial endocarditis and is seen in no other circumstances.

Summarizing the above paragraphs, we see that a classification of nephritis to be in accordance with modern knowledge must be elaborated from the following three main categories:

(A) The so-called Nephroses.
(B) The Glomerulo-nephritides.
(C) Arteriolo-sclerosis with its renal manifestations.

Detailed Classification.

If we proceed from this simple basis, we can distinguish various subdivisions on the following lines:

(A) The Nephroses

(1) *Lipoid Nephrosis*, probably a general disorder of metabolism, characterized by abnormal permeability of the cutaneous and renal vessels for albumins and lipoids. Massive albuminuria. Entire absence of cardio-vascular changes.

(2) *Nephropathies produced by poisons* such as corrosive sublimate, uranium, and chromates. Lesions almost entirely confined to the tubules. Oedema and albuminuria without cardio-vascular change. Usually

followed by complete healing with restitution of renal function. In very rare cases leading to permanent damage and secondary contraction of the kidney.

(3) *Amyloid Disease of the Kidney* falls into this class but need not be discussed in the present context.

(B) Glomerulo-nephritis.

(1) *Acute Diffuse Glomerulo-nephritis*, the classical nephritis appearing in the later weeks of an infectious fever. All the glomeruli are affected, the primary lesion being an acutely progressive swelling of the capillary endothelium of the glomeruli together with an accumulation of large numbers of leucocytes in the affected loops. Acute oedema, sometimes acute dilatation of the left heart with acute hypertonicity, albuminuria, haematuria, toxic lesions of the cutaneous and glomerular vessels. Uraemia may occur, complete resolution is possible (as in the examples of this disease which occurred so commonly during the war), but more frequently extension occurs with spread of the disease to the tubular apparatus, oedema becomes conspicuous owing to lesions of the cutaneous capillaries, and the continued hyperpiesis is followed by cardiac hypertrophy. If death occurs during any of these stages, post-mortem appearances of the kidney will range from a normal-looking though somewhat congested organ in which the microscope alone will reveal the disease of the glomerular capillaries, to a large smooth organ the size and pallor of which may either or both of them be conspicuous, according to the degree that swelling of the epithelial cells, or interstitial oedema, or fatty change, or haemorrhage into the renal substance, may have predominated.

(2) *Chronic Glomerulo-nephritis*, secondary contraction of the kidney. Variable albuminuria, repeated attacks of so-called 'renal' oedema, moderate to marked elevation

Table XIII

CLASSIFICATION OF NEPHRITIS.

A. The Nephroses	1. Lipoid Nephrosis. 2. Chemical nephropathies. 3. Amyloid disease.
B. Glomerulo-nephritis	1. Acute diffuse glomerulo-nephritis. 2. Chronic diffuse glomerulo-nephritis. 3. Focal glomerulo-nephritis. 4. Embolic glomerulo-nephritis.
C. Arteriolo-sclerosis	1. Pre-'nephritic' stage, 'essential hypertension'. 2. Later stage with cirrhosis of spleen and kidneys, renal failure, the so-called 'chronic interstitial nephritis'. 3. The malignant renal sclerosis of Fahr.

of the blood-pressure, cardiac hypertrophy, progressive destruction of the kidney substance, usually ends in renal failure and death from uraemia.

(3) *Focal Glomerulo-nephritis*, occurring perhaps most frequently as a complication of tonsillitis and other streptococcal infections. Marked haematuria, slight albuminuria, no oedema, no hypertension. Benign in course owing to the fact that a limited number of glomeruli only are affected. In very rare cases sufficient destruction may be produced to lead to secondary contraction of the kidney, with a clinical picture indistinguishable from the chronic diffuse glomerulo-nephritis.

(4) *Embolic Glomerulo-nephritis*, of academic interest as being the renal complication of infective endocarditis.

(C) Arteriolo-sclerosis.

(1 *a*) Essential hypertension, spasm of the arterioles producing high blood-pressure and later cardiac hypertrophy; apoplexy or cardiac failure may kill the patient, or a morbid change in the arterioles may progress to fibrosis producing its maximum effect on the abdominal glands, particularly the spleen and the kidneys, in which case the disease manifests itself as

(1 *b*) *Granular atrophy of the Kidneys*, the so-called chronic interstitial nephritis. Marked cardiac hypertrophy, albuminuria slight, oedema usually of cardiac origin, occasional death from renal failure though cardiac failure or cerebral disease following the morbid changes in the cerebral arterioles usually anticipate such an event.

(2) *The Malignant Renal Sclerosis of Fahr* is claimed by German authorities, such as Fahr and Aschoff, to be the cause of death from uraemia in the majority of the patients in whom arteriolo-sclerosis has produced marked renal cirrhosis. It is presumed by these

Table XIV

TO SHOW THE PRINCIPAL MANIFESTATIONS OF 'NEPHRITIS' OF DIFFERENT VARIETIES

	Oedema.	*Albuminuria.*	*Haematuria.*	*N. retention.*	*High blood-pressure.*
Lipoid Nephrosis.	++	++	−	−	−
Glomerulo-nephritis.					
A. Diffuse — Acute	+	+	+	−	+
A. Diffuse — Sub-acute	++	++	−	−	++
A. Diffuse — Chronic	+	+	−	+	++
B. Focal	+−	+	+	−	−
Arteriolo-sclerosis.					
Essential hypertension	−	−	−	−	++
Cirrhosis of kidney with renal failure	−	+−	−	+	++
Malignant sclerosis of Fahr	+	+	+−	+	++

The symbol + − indicates that the particular symptom or sign tends to, but does not invariably occur.

authorities that an accidental infection or intoxication has thrown a new and insuperable strain upon kidneys already damaged by vascular change.

The above in the opinion of the present writer presents a classification of nephritis which is compatible both with existing clinical and pathological knowledge. I can present it to the reader with the assurance that I have found it possible to harmonize it with the great majority of cases coming under my observation as a clinician. To pathologists who may find in it occasion for rebuke, I can but claim that it is in full accord with very recent writings by Professor Ludwig Aschoff, and leave them to produce opposing evidence more convincing than his.

CHAPTER VI

THE TREATMENT OF NEPHRITIS

The previous chapters of this book have tended to demonstrate the magnitude of the problems which await solution before we can profess to have an adequate knowledge of the diseases grouped under the heading of nephritis. It may in consequence appear illogical to attempt to lay down any rules of treatment in conditions which are still so obscure. But even if we admit that our present methods are largely empirical and often unsatisfactory, experience has shown that it is possible to obtain better results by following certain rules than by ignoring them or by haphazard methods in each case encountered.

At the outset it is of paramount value to form at least a working diagnosis, on the lines indicated in the preceding chapter, as to the exact nature of the case; that is to say, whether it is *acute* or *chronic*, whether it is an example of *pure nephrosis*, of *glomerulo-nephritis*, or of *arteriolo-sclerosis with renal manifestations*, and whether *renal failure* is present as a *transitory* or as a *permanent* phenomenon.

Simultaneously the practitioner is called upon to decide what manifestation of the disease he is going to combat in the first place, whether he is going to endeavour to tide the patient over an attack of actual or threatened *uraemia*, whether he is going to attempt to relieve *oedema*, or whether *hypertension* calls for active immediate treatment.

In order to make practical reference easy, I have arranged this final chapter in sections which correspond to preceding chapters, hoping that useful information may thus be easily found by those engaged in the active treatment of these conditions.

§ I. The Treatment of Uraemia

It is often laid down that the treatment of uraemia aims at the elimination of toxins from the blood. The chapter

dealing with this condition tends to demonstrate that 'uraemia' implies a profound disturbance of the chemistry of the body fluids as a result of a failure of the kidneys to perform their normal functions. The evidence in favour of the presence of toxins, in the sense of foreign and poisonous chemical substances, is absent or deficient, the hyperpnoea, the convulsions, the vomiting, and the coma of uraemia being more readily explicable by changes in the proportionate presence of substances which are present even in physiological states.

When treatment in uraemia aims at promoting excretion by subsidiary channels it is logical. The bowels must be made to act thoroughly and regularly, a *strong purgative* at the outset is often essential, and full doses of *saline or vegetable cathartics* are usually necessary afterwards. Mercurial purgatives, such as calomel, are contra-indicated because if they reach the blood-stream they will tend to exert an adverse influence on the kidney. Excretion by the skin should be promoted whenever anuria or oliguria indicates that water-retention may occur. *Sweating* should be encouraged by warm sponging or wet packs, or hot-air baths may prove valuable. The latter method should be employed with caution whenever the patient's condition is weak, as in the event of sweating not occurring quickly hot-air baths may prove very exhausting. This applies particularly in cases with hypertension and cardiac changes.

Venesection has often been advocated, sometimes with simultaneous transfusion with normal saline. Depending as it does on the theory that toxins are present which must be diluted or eliminated, this method seldom has either theoretical or practical advantage. In cases with cardio-vascular complications, venesection is, however, sometimes of value.

Lumbar puncture is often desirable for diagnostic purposes, and in cases exhibiting hypertension and coma it is often a valuable therapeutic measure. If the cerebrospinal fluid is under tension lumbar puncture should be repeated at two-hourly intervals.

DRUGS OF UTILITY IN URAEMIA

For Producing Catharsis.

Pulv. Jalapae Co. 1 dr. (fresh powder) to be followed by full doses of magnesium sulphate.

Pil. Colocynth. Co. B.P. . . 4–8 grains.
Pil. Rhei Co. B.P. . . . 4–8 grains.
(In coma) Croton Oil . . . 1 minim in butter.

For Restoring Alkali Reserve.

Sodium bicarbonate in doses of 1 dr. hourly.

For Restoring Calcium Shortage.

Calcium chloride, gr. 1 in distilled water 40 minims, to be given deeply into the muscles hourly for 4–5 doses, or to be given intravenously in a dose of 5 grains in 30 c.cm. of normal saline.

For the Relief of Cerebral Oedema.

40 c.cm. of a 30 per cent. solution of sodium chloride to be given intravenously.

For Promoting Sweating (seldom permissible).

Pilocarpine nitrate gr. $\frac{1}{4}$ in sterile water 8 minims, to be injected subcutaneously.

Certain special **symptoms** of uraemia call for particular treatment. When repeated blood analysis is possible the physician is able to correct chemical disturbances with greater exactitude, but even in the absence of such control the following therapeutic indications are of practical importance.

Hyperpnoea, in the absence of pulmonary and cardiac complications, is usually indicative of lowering of the alkali reserve of the blood, this should be corrected by the administration of sodium bicarbonate in doses up to 1 drachm hourly.

Twitching and convulsions suggest calcium shortage and are an indication for the administration of calcium in addition to other forms of treatment. This is best given in the form of intramuscular injections of calcium chloride 1 gr. dissolved in 40 mm. of distilled water, repeated hourly for four or five doses. In extreme cases a dose of 5 grs. in 30 c.cm. of normal saline may be given intravenously.

Coma is in some cases suggestive of acute cerebral oedema, and, if this hypothesis is entertained, it is an indication for the administration of hypertonic saline with a view to reducing the intracerebral pressure. 40 c.cm. of a 30 per cent. solution of sodium chloride given intravenously has in many cases been responsible for a return to consciousness.

§ II. The Treatment of Oedema

Oedema in nephritis has been shown in preceding chapters to be the result of several factors and to occur in several distinct varieties.

Cardiac oedema is met with not infrequently in patients in whom prolonged hypertension has become complicated by heart failure. The treatment of oedema of this type will not be discussed here.

The so-called *'renal' oedema* is met with both in pure nephrosis and in glomerulo-nephritis in its various manifestations, and in order that treatment may be both safe and

Table XV

DIET IN NEPHROSIS (Modified from Epstein)

Protein g. 120–40. Carbohydrate g. 150–300. Fat g. 20–40.
Total calories: 1,250–2,500.

Lean meat or ham, oysters, fish. Whites of eggs. Broad beans, peas, lentils, rice, oatmeal. Fruits, including especially bananas.
Tea, coffee, or cocoa. Skimmed milk.
Avoid as far as possible: fat, cream, oil, butter, egg yolk.

BREAKFAST.	LUNCH.	DINNER.
Porridge	Fish or lean ham	Lentil or pea soup
Fish	Curry and rice	Oysters
White of egg poached	Salad	Lean meat, hot or cold
Toast, honey, marmalade	Vegetables	Vegetables
Tea or coffee	Bananas	Haddock or mushroom savoury
Skimmed milk	Stewed apple with whipped white of egg	

effective it is necessary to have a clear conception of the correct diagnosis in each particular case.

In *pure nephrosis* there are no cardio-vascular changes and no evidence of inability on the part of the kidney to excrete nitrogenous substances. A diet rich in nitrogen is, therefore, not only without danger but helpful for the reasons indicated by the work of Epstein. In the preceding table will be found set out a modification adapted for British patients of the diet recommended by Epstein. In addition to this such cases can suitably be treated by the administration of **urea** in doses of from 15–100 grs. per diem given in capsules. It should further be noted that an essential feature of the treatment advocated by Epstein is the administration of thyroid extract. This should be given at first cautiously in doses up to 5 grs. per diem, and if, as is usually the case, no signs of hyperthyroidism, such as increased pulse-rate, become evident, the dose should be increased and may sometimes be given in a quantity as great as 60 grs. daily without any adverse effect.

According to Epstein the first indication of benefit from this treatment is a reduction in the cholesterol content of the blood, and in all cases frequent blood analysis is desirable in the course of this treatment in order that the physician may be certain that the nitrogenous constituents of the blood are not rising as a result of the ingestion of nitrogenous bodies in large quantities. It has been sufficiently laid down in earlier chapters that pure nephrosis is a somewhat rare condition, and it cannot be emphasized too strongly that this treatment is designed for such cases and for such cases alone.

In *glomerulo-nephritis* oedema is a frequent manifestation, and it must be borne in mind that even if hypertension and nitrogen retention are not demonstrable they are liable to make their appearance in later stages whenever this condition is present. Diets containing abundant protein and the administration of urea must, therefore, be employed with extreme caution, if at all, and other means of combating

Table XVI

SALT-FREE DIET

Main Articles of Food to be Avoided:

Ham, bacon, tongue, and all smoked or salted meat or fish.

Bread, cake, and biscuits unless made at home without salt.

Cheese of all sorts. Milk.

Butter, unless unsalted.

Shell-fish.

Permitted Foods:

Home-made bread and scones, baked without salt.

Tea, coffee, cocoa with cream.

Unsalted butter. Jam, honey, marmalade.

Unsalted meat or fish. Eggs.

Fresh fruits, raw or cooked.

Salads and raw vegetables.

All vegetables which have been cooked in several changes of unsalted water.

No salt must be employed in cooking.

Unleavened bread, made without salt, can be widely obtained from Jewish caterers and restaurants.

oedema are perhaps more desirable. Of these a *salt-free* diet should, perhaps by reason of the claims made for it in the past, be the first method of treatment to be attempted. Details of such a diet are to be found in Table XVI and again in Table XVIII, the latter being an example of a diet which is not only salt-free when carefully prepared, but containing so small an amount of protein that it may be given in comparative safety, even when renal failure is obviously present or threatened.

In Table XVII will be found set out the foods which according to the observations of Sansum, Blatherwick and Smith tend to influence the reaction of the urine, and in Table XVIII are certain menus after consideration of which the practitioner can select a diet tending to alter the reaction of the urine in whichever direction may be desired. It will be observed that the application of a salt-free low-nitrogen diet can readily be made to tend to produce an alkaline urine, and this is desirable in all cases such as those at present under discussion.

In the event of a failure to reduce oedema by measures such as those hitherto suggested, the treatment with alkalis suggested by Osman may be instituted. Details of this treatment are to be found on page 79. Large doses of an alkaline mixture are given in increasing amounts until the urine is made alkaline. *Tetany* has occasionally appeared as a complication of this treatment and should be treated on the lines shown in the Table.

Diuretics are, in my opinion, very seldom, if ever, indicated in the treatment of true renal oedema. Their success is almost entirely confined to cases of nephrosis or of cardiac oedema. If the kidney is relatively undamaged they may be safely used, but if it is the site of inflammation, whether acute or chronic, they should be used with great caution.

Table XVII

FOODS TENDING TO INFLUENCE THE REACTION OF THE URINE

(Figures represent total excess of acid over base, or vice versa, in c.cm. normal per 100 grammes.)

Acid-producing Foods.		Alkali-producing Foods.	
Bread, white	2·7	Milk	2·3
Bread, wholemeal	3·0	*Oranges	5·6
Water biscuits	7·8	Melon	7·5
Oatmeal	13·0	Peaches	5·0
Rice	8·0	Lemons	5·4
Eggs	11·1	*Apples	3·8
Egg-white	5·2	*Bananas	5·5
Egg-yolk	26·7	Beans, dried	23·8
Average fish	15·0	Cabbage	4·3
Average meat	14·0	Carrots	10·8
Chicken	17·0	Cauliflower	5·3
Oysters	30·0	Celery	5·3
		Chestnuts	7·4
		Lettuce	7·3
		Peas, dried	7·0
		Radishes	2·8
		*Potatoes	7·2

* Specially efficient.

Table XVIII

ACID-PRODUCING DIET

BREAKFAST.	LUNCH.	DINNER.
Porridge	Smoked salmon	Oysters
Scrambled yolks of eggs	Omelette or fish	Petite marmite
Fish	Steak or curry	Roast chicken without vegetables
Wholemeal bread and butter	Biscuits & cheese	Baked custard
		Savoury

ALKALI-PRODUCING DIET

BREAKFAST.	LUNCH.	DINNER.
Orange or grapefruit	Radishes or melon	Vegetable soup (Pea)
Bread and milk	Chestnut, potato, and Brussels sprouts stew	Baked beans with tomato sauce
Sultana scone with butter and honey	Celery and apple salad	Green salad
Milky coffee	Banana fritters	Stewed apple with white of egg
		Fruit

Table XIX

TREATMENT OF NEPHRITIS WITH OEDEMA BY ALKALIS. (Osman)

Stock Mixture:

Potassium citrate Potassium bicarbonate Sodium citrate Sodium bicarbonate	aa gr. xv
Aqua menth. pip. Aqua chlorof.	aa ad 1 oz.

Daily dose of alkali to be given is 180 grains of total alkali, increasing by 60–100 grains daily until the urine is alkaline with a pH of 7·0–7·6. This will require often a total dosage of 1,000 grains daily. The increase must be pressed in spite of increasing oedema as shown by the weight rising, alkalinity of the urine being the one criterion of sufficient dosage.

Full dosage, to be maintained until oedema has quite disappeared, when the alkali may be cautiously reduced by 100 grains every three days.

If *tetany* occurs reduce dose temporarily by one-third of total and give 1 grain calcium chloride in 40 minims distilled water intramuscularly every two hours for several doses.

§ III. The Treatment of High Blood-pressure associated with Nephritis

The treatment of *hypertension* scarcely falls within the orbit of the present book. Arteriolo-sclerosis, essential hypertension, is a disease which exists for years before there is any evidence of the kidneys being affected. A toxic factor is generally regarded as being present and should be sought for and eliminated whenever possible. Rest, produced by physical methods or by the administration of certain drugs, is usually the all-important factor in the treatment. *Cardiac complications* call for treatment as they arise, but will not be discussed in this volume.

Renal failure is the outstanding effect of chronic arteriolo-sclerosis calling for mention in this chapter. Its treatment is similar to the treatment of renal failure arising in other circumstances and consists of:

(*a*) The provision of a diet which calls for the minimum of work on the part of the kidney;

and (*b*) The treatment of uraemia whenever it arises or is threatened.

Diet in renal failure should be designed to give the patient no more protein than is required to replace that inevitable wear and tear of protoplasm which incessantly occurs during life. It is scarcely necessary to say that this minimum is something very much lower than the diet which the ordinary person is accustomed to take; there seems, indeed, little doubt that life can be maintained and health preserved for very long periods on a daily diet containing 30 grammes of protein or less. In Table XX and Table XXI will be found analyses of the more commonly occurring foods in which the relative amount of protein is low. A short study of these tables will show the reader that although low-protein foods have usually been selected for inclusion, there is still an enormous variation between individual items: thus, 2½ oz.

Table XX

FOR CONSTRUCTING LOW-PROTEIN DIETS

Each of the common foods given below contains 5 grammes of protein in the weight stated; the grammes of carbohydrate and fat in such amounts are also stated. Unless otherwise stated figures refer to cooked foods.

	Prot.	*Carb.*	*Fat.*
1⅔ oz. Bread, white	5	25	0
3⅓ oz. Bread, brown	5	50	0
1¼ oz. Biscuit, average unsweetened	5	25	0
8 oz. Potato, boiled	5	50	0
3½ oz. Potato, fried in fat	5	50	40
5 oz. Carrots	5	25	0
24 oz. Turnips	5	15	0
15 oz. Cabbage	5	15	0
15 oz. Spinach	5	15	0
20 oz. Cauliflower	5	15	0
12 oz. Lettuce, raw	5	10	1
25 oz. Celery, raw	5	25	0
20 oz. Tomato, raw or cooked	5	25	0
30 oz. Marrow, vegetable	5	50	0
2½ oz. Peas, green	5	10	1
2½ oz. Peas, dried	5	12	0
8 oz. Asparagus	5	7	0
1¼ Oatmeal, raw	5	25	5
12 oz. Quaker Oats	5	25	3
½ oz. Partridge	5	0	0
½ oz. Pheasant	5	0	0
⅔ oz. Beef, Mutton, Pork, Veal, Chicken, Duck — average roast	5	0	½–5
¾ oz. Liver	5	1	2
1 oz. Kidney	5	0	1½
⅔ oz. Cheese, average	5	0	6
½ oz. Cheese, Dutch	5	0	2
⅔ oz. Cheese, full cream	5	0	8
2½ oz. Oysters, raw, without shell	5	3	0
1 oz. Lobster	5	0	½
¾ oz. Salmon	5	0	2½
1 oz. Sole	5	0	0
1¼ oz. Plaice	5	0	½
1 oz. Mackerel	5	0	2

of green peas contain the same amount of protein as is given by 25 oz. of celery or 24 oz. of turnips, and it is, therefore, not sufficient to advise the patient to choose a vegetarian diet in preference to one containing meat, but details should be given as to which vegetables may be the more desirable. The foods in Table XX are for the most part almost free of protein, and in constructing a diet such should be selected in the first place to constitute the greater part of the daily ration. Palatability and variety should then be secured by adding a limited number of items from amongst those shown in the Table. In Table XXII will be found set out in detail a specimen menu suitable for many cases of renal failure. This must not for a moment be adopted as a standard diet, but it is hoped that by studying it the reader may be able to devise diets for himself by the application of the principles laid down above, and by reference to the detailed analysis of foods supplied in the other tables.

§ IV. The Treatment of Nephritis according to the Variety of the Disease Encountered

This has already been dealt with in preceding sections; but at the risk of some repetition the matter may be reconsidered as follows:

1. *Nephrosis.* The treatment here is largely a question of treating oedema and has been described under that heading. If, as has been suggested, thyroid medication has a specific effect in lipoid nephrosis, it must be used in every case.

2. *Glomerulo-nephritis* requires some special discussion. Whether of the acute diffuse, the chronic, or the focal type, glomerulo-nephritis includes practically all cases of true primary renal inflammation, and is a disease of such gravity that no therapeutic measure which may be of real assistance must be neglected.

Diffuse glomerulo-nephritis is the most serious variety, and arising as it does usually as a complication of an infectious

Table XXI

FOR CONSTRUCTING LOW-PROTEIN DIETS

To be used in conjunction with preceding table. The protein-content of the foods in this table is generally very low; the analysis of each, in grammes, is shown.

	Prot.	*Carb.*	*Fat.*
3 oz. Apples, raw	0	10	0
5 oz. Apples, stewed, without sugar	0	10	0
4 oz. Banana, without skin	0	15	0
3 oz. Cherries, raw, with stones	1	10	0
3 oz. Coco-nut, fresh	5	8	40
4 oz. Dates	0	20	0
1 oz. Figs, stewed	0	15	0
4 oz. Grape-fruit, with skin	½	5	0
4 oz. Grapes	2	20	0
6 oz. Melon, with skin	½	5	0
4 oz. Oranges, with skin	1	10	0
6 oz. Peaches, fresh	1	10	0
3 oz. Pears	0	10	0
4 oz. Pineapple, fresh	1	10	0
3 oz. Raspberries	1	10	0
6 oz. Rhubarb, stewed	0	5	0
5 oz. Strawberries	1	12	0
5 oz. Milk, fresh	5	8	5
1 oz. Cream, average	0	0	5
1 oz. Olive Oil	0	0	30
1 oz. Butter	0	0	30
1 average hen's egg	6	0	5½
White of 1 egg	3½	0	0
Yolk of 1 egg	2½	0	5½
1 oz. Honey	0	25	0
1 oz. Jam, average	0	20	0

fever, *prophylactic measures*, if feasible, must not be neglected. The work of Osman and others, who claim that the administration of alkalis during such fevers leads to an important diminution in the number of cases attacked by this disease, is at present unproved, but clearly of great significance. The present writer does not hesitate to support this treatment wholeheartedly. In real practice it amounts to the giving of bicarbonate and citrate during the first three or four weeks of any severe infectious fever in sufficient dosage to make the urine just alkaline. The type of diet selected for such cases in general is one which tends to make the urine at most slightly acid and, accordingly, large doses of alkali are neither required nor desirable. The treatment appears to be entirely without risk.

When diffuse nephritis is already definitely present, treatment should consist of an attempt to eradicate or neutralize the bacterial toxins responsible, and also to place the kidney in a position most favourable for healing. The first of these objects is rarely obtainable. The possible value of an appropriate streptococcal serum should be kept in mind. Vaccines and antigens in general are unlikely to be of benefit in cases where acute inflammation is already tending to swamp the patient with toxin, and the use of mercurochrome and other substances, for which it is claimed that they possess powers of local antisepsis, is, in my opinion, without value. Occasionally cases are met with in which the streptococcal infection clearly arises from some source, such as the tonsil, and these foci should be eliminated whenever possible. It, must, however, be borne in mind that such treatment can, at best, prevent the further ingress of toxin and does nothing to affect the organ in its existing state of inflammation.

The affected kidney can be placed in a situation best calculated to assist recovery by securing for it the maximum of *rest*. It is impossible to achieve complete rest, just as it is impossible to achieve rest for an infected myocardium or for a pyloric antrum which is affected by ulceration, but there

Table XXII

SPECIMEN OF DIET IN RENAL FAILURE

Breakfast

Grape-fruit 3 oz.
Porridge made from ⅓ oz. dry oatmeal.
Cream (top milk) 2 oz.
One large cream cracker, or Ryvita biscuit.
Butter ½ oz., Honey, jam, or marmalade.
Tea or coffee with cream and sugar.

Lunch

Boiled carrots 3 oz. fried in butter ½ oz.
Tomato and lettuce 4 oz.
Flavoured with oil 2 oz., lemon-juice or vinegar, pepper.
Ice-cream 3 oz.

Dinner

Vegetable soup, carrots, turnips, and cabbage.
Hot tomatoes stuffed with nuts, onion, and breadcrumbs 3 oz.
Orange and lettuce salad with mayonnaise 4 oz.
Three bran wafers with butter and cream cheese 1 oz.

The above diet is practically salt-free and contains approximately 3,000 calories with not more than 10 grammes of protein.

is a clear indication for limiting the food intake to the minimum necessary for the maintenance of nitrogenous equilibrium. It is probable that the elimination of water by the kidney is not in itself attended by the performance of much work. It seems, indeed, that the concentration of nitrogenous substances and phosphates represents the major part of the work performed by the organ. These substances should, therefore, be strictly controlled in the ingested food, and a suitable diet can readily be worked out from the Tables supplied in an earlier part of this chapter. The remaining important consideration is that of the reaction of the urine, and again we must face the fact that a faintly alkaline urine is the one which probably represents the minimum degree of renal activity. Foods should, therefore, be selected which will tend to produce such a reaction and, if necessary, small doses of potassium citrate and sodium bicarbonate may be given for the same purpose.

In *chronic glomerulo-nephritis* the problems are not essentially different. Certain symptoms, such as oedema, or uraemia, may call for special treatment, the lines of which have already been laid down.

In *focal glomerulo-nephritis* the diagnosis connotes the presence of a primary source of infection elsewhere. This calls for treatment, and the renal manifestations are usually so mild that in themselves they do not require any special attention. If it so happen that the degree of renal involvement has been very severe, treatment should be on the lines indicated for diffuse glomerulo-nephritis.

Embolic glomerulo-nephritis is a complication occurring in infective endocarditis, and until a successful treatment for this disease has been evolved, it is superfluous to consider therapeutic measures in regard to this renal manifestation.

3. *Arteriolo-sclerosis*, as has already been shown, may cause renal failure, the treatment of which has already been discussed. The malignant sclerosis of Fahr, being of the nature of an acute nephritis affecting a kidney already damaged by

arteriolo-sclerosis, can only be treated on the lines already laid down in connexion with renal failure and acute glomerulo-nephritis. Apart from this the treatment of this disease is the treatment of essential hypertension, or of its complications, such as cardiac failure, and is not appropriate for discussion in the present work.

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